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FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER **PT-1066 USN** U.S. APPLICATION NO (If known, see 37 CFR 1.5) TO BE ASSIGNED 10/089128
INTERNATIONAL APPLICATION NO. PCT/US00/25643	INTERNATIONAL FILING DATE 19 September 2000	PRIORITY DATE CLAIMED 23 September 1999

TITLE OF INVENTION
MOLECULES FOR DIAGNOSTICS AND THERAPEUTICS

APPLICANT(S) FOR DO/EO/US
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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is the **FIRST** submission of items concerning a filing under 35 U.S C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to promptly begin national examination procedures (35 U.S C. 371 (f)).
4. ☐ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31)
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau)
   b. ☐ has been communicated by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b ☐ have been communicated by the International Bureau.
   c. ☐ have not been made, however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
   e. ☐ attached hereto Article 34 Amendment
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.27 and 3.31 is included.
13. ☐ A FIRST preliminary amendment
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

1) Transmittal Letter (2 pp, in duplicate)
2) Return Postcard
3) Express Mail Label No.: EL 856 149 234 US
4) Sequence Listing on Diskette
5) Sequence Listing Statement
6) Copy of International Search Report (PCT/ISA/210)

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) TO BE ASSIGNED	INTERNATIONAL APPLICATION NO.: PCT/US00/25643	ATTORNEY'S DOCKET NUMBER PT-1066 USN

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17. ☒ The following fees are submitted.

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.......$1000 00

☐International preliminary examination fee (37 CFR 1 482) not paid to USPTO but International Search Report prepared by the EPO or JPO..$860 00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..$710.00

☒**International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)..........$710.00**

☐International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4).......... . . . $100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =				$710.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	19 =	0	**X $ 18.00**	$	
Independent Claims	1 =	0	**X $ 80.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			**+ $270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$	
SUBTOTAL =				$710.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1492(f)). +				$	
TOTAL NATIONAL FEE =				$710.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by the appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					
TOTAL FEES ENCLOSED =				$710.00	
				Amount to be Refunded:	$
				Charged:	$

a. ☐ A check in the amount of $________ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 09-0108 in the amount of $710.00 to cover the above fees.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 09-0108. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO.

INCYTE GENOMICS, INC.
3160 Porter Drive
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SIGNATURE

NAME: Diana Hamlet-Cox

REGISTRATION NUMBER. 33,302

DATE: 22 March 2002

MOLECULES FOR DIAGNOSTICS AND THERAPEUTICS

TECHNICAL FIELD

The present invention relates to human molecules and to the use of these sequences in the diagnosis, study, prevention, and treatment of diseases associated with, as well as effects of exogenous compounds on, the expression of human molecules.

BACKGROUND OF THE INVENTION

The human genome is comprised of thousands of genes, many encoding gene products that function in the maintenance and growth of the various cells and tissues in the body. Aberrant expression or mutations in these genes and their products is the cause of, or is associated with, a variety of human diseases such as cancer and other cell proliferative disorders, autoimmune/inflammatory disorders, infections, developmental disorders, endocrine disorders, metabolic disorders, neurological disorders, gastrointestinal disorders, transport disorders, and connective tissue disorders. The identification of these genes and their products is the basis of an ever-expanding effort to find markers for early detection of diseases, and targets for their prevention and treatment. Therefore, these genes and their products are useful as diagnostics and therapeutics. These genes may encode, for example, enzyme molecules, molecules associated with growth and development, biochemical pathway molecules, extracellular information transmission molecules, receptor molecules, intracellular signaling molecules, membrane transport molecules, protein modification and maintenance molecules, nucleic acid synthesis and modification molecules, adhesion molecules, antigen recognition molecules, secreted and extracellular matrix molecules, cytoskeletal molecules, ribosomal molecules, electron transfer associated molecules, transcription factor molecules, chromatin molecules, cell membrane molecules, and organelle associated molecules.

For example, cancer represents a type of cell proliferative disorder that affects nearly every tissue in the body. A wide variety of molecules, either aberrantly expressed or mutated, can be the cause of, or involved with, various cancers because tissue growth involves complex and ordered patterns of cell proliferation, cell differentiation, and apoptosis. Cell proliferation must be regulated to maintain both the number of cells and their spatial organization. This regulation depends upon the appropriate expression of proteins which control cell cycle progression in response to extracellular signals such as growth factors and other mitogens, and intracellular cues such as DNA damage or nutrient starvation. Molecules which directly or indirectly modulate cell cycle progression fall into several categories, including growth factors and their receptors, second messenger and signal transduction proteins, oncogene products, tumor-suppressor proteins, and mitosis-promoting factors.

Aberrant expression or mutations in any of these gene products can result in cell proliferative disorders such as cancer. Oncogenes are genes generally derived from normal genes that, through abnormal expression or mutation, can effect the transformation of a normal cell to a malignant one (oncogenesis). Oncoproteins, encoded by oncogenes, can affect cell proliferation in a variety of ways and include growth factors, growth factor receptors, intracellular signal transducers, nuclear transcription factors, and cell-cycle control proteins. In contrast, tumor-suppressor genes are involved in inhibiting cell proliferation. Mutations which cause reduced function or loss of function in tumor-suppressor genes result in aberrant cell proliferation and cancer. Although many different genes and their products have been found to be associated with cell proliferative disorders such as cancer, many more may exist that are yet to be discovered.

DNA-based arrays can provide a simple way to explore the expression of a single polymorphic gene or a large number of genes. When the expression of a single gene is explored, DNA-based arrays are employed to detect the expression of specific gene variants. For example, a p53 tumor suppressor gene array is used to determine whether individuals are carrying mutations that predispose them to cancer. A cytochrome p450 gene array is useful to determine whether individuals have one of a number of specific mutations that could result in increased drug metabolism, drug resistance or drug toxicity.

DNA-based array technology is especially relevant for the rapid screening of expression of a large number of genes. There is a growing awareness that gene expression is affected in a global fashion. A genetic predisposition, disease or therapeutic treatment may affect, directly or indirectly, the expression of a large number of genes. In some cases the interactions may be expected, such as when the genes are part of the same signaling pathway. In other cases, such as when the genes participate in separate signaling pathways, the interactions may be totally unexpected. Therefore, DNA-based arrays can be used to investigate how genetic predisposition, disease, or therapeutic treatment affects the expression of a large number of genes.

Enzyme Molecules

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, and SEQ ID NO:8 encode, for example, human enzyme molecules.

The cellular processes of biogenesis and biodegradation involve a number of key enzyme classes including oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. These enzyme classes are each comprised of numerous substrate-specific enzymes having precise and well regulated functions. These enzymes function by facilitating metabolic processes such as glycolysis, the tricarboxylic cycle, and fatty acid metabolism; synthesis or degradation of amino acids, steroids, phospholipids, alcohols, etc.; regulation of cell signalling, proliferation, inflamation, apoptosis, etc.,

and through catalyzing critical steps in DNA replication and repair, and the process of translation.

Oxidoreductases

Many pathways of biogenesis and biodegradation require oxidoreductase (dehydrogenase or reductase) activity, coupled to the reduction or oxidation of a donor or acceptor cofactor. Potential cofactors include cytochromes, oxygen, disulfide, iron-sulfur proteins, flavin adenine dinucleotide (FAD), and the nicotinamide adenine dinucleotides NAD and NADP (Newsholme, E.A. and A.R. Leech (1983) Biochemistry for the Medical Sciences, John Wiley and Sons, Chichester, U.K., pp. 779-793). Reductase activity catalyzes the transfer of electrons between substrate(s) and cofactor(s) with concurrent oxidation of the cofactor. The reverse dehydrogenase reaction catalyzes the reduction of a cofactor and consequent oxidation of the substrate. Oxidoreductase enzymes are a broad superfamily of proteins that catalyze numerous reactions in all cells of organisms ranging from bacteria to plants to humans. These reactions include metabolism of sugar, certain detoxification reactions in the liver, and the synthesis or degradation of fatty acids, amino acids, glucocorticoids, estrogens, androgens, and prostaglandins. Different family members are named according to the direction in which their reactions are typically catalyzed; thus they may be referred to as oxidoreductases, oxidases, reductases, or dehydrogenases. In addition, family members often have distinct cellular localizations, including the cytosol, the plasma membrane, mitochondrial inner or outer membrane, and peroxisomes.

Short-chain alcohol dehydrogenases (SCADs) are a family of dehydrogenases that only share 15% to 30% sequence identity, with similarity predominantly in the coenzyme binding domain and the substrate binding domain. In addition to the well-known role in detoxification of ethanol, SCADs are also involved in synthesis and degradation of fatty acids, steroids, and some prostaglandins, and are therefore implicated in a variety of disorders such as lipid storage disease, myopathy, SCAD deficiency, and certain genetic disorders. For example, retinol dehydrogenase is a SCAD-family member (Simon, A. et al. (1995) J. Biol. Chem. 270:1107-1112) that converts retinol to retinal, the precursor of retinoic acid. Retinoic acid, a regulator of differentiation and apoptosis, has been shown to down-regulate genes involved in cell proliferation and inflammation (Chai, X. et al. (1995) J. Biol. Chem. 270:3900-3904). In addition, retinol dehydrogenase has been linked to hereditary eye diseases such as autosomal recessive childhood-onset severe retinal dystrophy (Simon, A. et al. (1996) Genomics 36:424-430).

Propagation of nerve impulses, modulation of cell proliferation and differentiation, induction of the immune response, and tissue homeostasis involve neurotransmitter metabolism (Weiss, B. (1991) Neurotoxicology 12:379-386; Collins, S.M. et al. (1992) Ann. N.Y. Acad. Sci. 664:415-424; Brown, J.K. and H. Imam (1991) J. Inherit. Metab. Dis. 14:436-458). Many pathways of neurotransmitter metabolism require oxidoreductase activity, coupled to reduction or oxidation of a

cofactor, such as NAD^+/NADH (Newsholme, E.A. and A.R. Leech (1983) Biochemistry for the Medical Sciences, John Wiley and Sons, Chichester, U.K. pp. 779-793). Degradation of catecholamines (epinephrine or norepinephrine) requires alcohol dehydrogenase (in the brain) or aldehyde dehydrogenase (in peripheral tissue). NAD^+-dependent aldehyde dehydrogenase oxidizes 5-hydroxyindole-3-acetate (the product of 5-hydroxytryptamine (serotonin) metabolism) in the brain, blood platelets, liver and pulmonary endothelium (Newsholme, supra, p. 786). Other neurotransmitter degradation pathways that utilize NAD^+/NADH-dependent oxidoreductase activity include those of L-DOPA (precursor of dopamine, a neuronal excitatory compound), glycine (an inhibitory neurotransmitter in the brain and spinal cord), histamine (liberated from mast cells during the inflammatory response), and taurine (an inhibitory neurotransmitter of the brain stem, spinal cord and retina) (Newsholme, supra, pp. 790, 792). Epigenetic or genetic defects in neurotransmitter metabolic pathways can result in a spectrum of disease states in different tissues including Parkinson disease and inherited myoclonus (McCance, K.L. and S.E. Huether (1994) Pathophysiology, Mosby-Year Book, Inc., St. Louis MO, pp. 402-404; Gundlach, A.L. (1990) FASEB J. 4:2761-2766).

Tetrahydrofolate is a derivatized glutamate molecule that acts as a carrier, providing activated one-carbon units to a wide variety of biosynthetic reactions, including synthesis of purines, pyrimidines, and the amino acid methionine. Tetrahydrofolate is generated by the activity of a holoenzyme complex called tetrahydrofolate synthase, which includes three enzyme activities: tetrahydrofolate dehydrogenase, tetrahydrofolate cyclohydrolase, and tetrahydrofolate synthetase. Thus, tetrahydrofolate dehydrogenase plays an important role in generating building blocks for nucleic and amino acids, crucial to proliferating cells.

3-Hydroxyacyl-CoA dehydrogenase (3HACD) is involved in fatty acid metabolism. It catalyzes the reduction of 3-hydroxyacyl-CoA to 3-oxoacyl-CoA, with concomitant oxidation of NAD to NADH, in the mitochondria and peroxisomes of eukaryotic cells. In peroxisomes, 3HACD and enoyl-CoA hydratase form an enzyme complex called bifunctional enzyme, defects in which are associated with peroxisomal bifunctional enzyme deficiency. This interruption in fatty acid metabolism produces accumulation of very-long chain fatty acids, disrupting development of the brain, bone, and adrenal glands. Infants born with this deficiency typically die within 6 months (Watkins, P. et al. (1989) J. Clin. Invest. 83:771-777; Online Mendelian Inheritance in Man (OMIM), #261515). The neurodegeneration that is characteristic of Alzheimer's disease involves development of extracellular plaques in certain brain regions. A major protein component of these plaques is the peptide amyloid-β (Aβ), which is one of several cleavage products of amyloid precursor protein (APP). 3HACD has been shown to bind the Aβ peptide, and is overexpressed in neurons affected in Alzheimer's disease. In addition, an antibody against 3HACD can block the toxic effects of Aβ in a cell culture model of Alzheimer's disease (Yan, S. et al. (1997) Nature 389:689-695; OMIM,

#602057).

Steroids, such as estrogen, testosterone, corticosterone, and others, are generated from a common precursor, cholesterol, and are interconverted into one another. A wide variety of enzymes act upon cholesterol, including a number of dehydrogenases. Steroid dehydrogenases, such as the hydroxysteroid dehydrogenases, are involved in hypertension, fertility, and cancer (Duax, W.L. and D. Ghosh (1997) Steroids 62:95-100). One such dehydrogenase is 3-oxo-5-α-steroid dehydrogenase (OASD), a microsomal membrane protein highly expressed in prostate and other androgen-responsive tissues. OASD catalyzes the conversion of testosterone into dihydrotestosterone, which is the most potent androgen. Dihydrotestosterone is essential for the formation of the male phenotype during embryogenesis, as well as for proper androgen-mediated growth of tissues such as the prostate and male genitalia. A defect in OASD that prevents the conversion of testosterone into dihydrotestosterone leads to a rare form of male pseudohermaphroditis, characterized by defective formation of the external genitalia (Andersson, S. et al. (1991) Nature 354:159-161; Labrie, F. et al. (1992) Endocrinology 131:1571-1573; OMIM #264600). Thus, OASD plays a central role in sexual differentiation and androgen physiology.

17β-hydroxysteroid dehydrogenase (17βHSD6) plays an important role in the regulation of the male reproductive hormone, dihydrotestosterone (DHTT). 17βHSD6 acts to reduce levels of DHTT by oxidizing a precursor of DHTT, 3α-diol, to androsterone which is readily glucuronidated and removed from tissues. 17βHSD6 is active with both androgen and estrogen substrates when expressed in embryonic kidney 293 cells. At least five other isozymes of 17βHSD have been identified that catalyze oxidation and/or reduction reactions in various tissues with preferences for different steroid substrates (Biswas, M.G. and D.W. Russell (1997) J. Biol. Chem. 272:15959-15966). For example, 17βHSD1 preferentially reduces estradiol and is abundant in the ovary and placenta. 17βHSD2 catalyzes oxidation of androgens and is present in the endometrium and placenta. 17βHSD3 is exclusively a reductive enzyme in the testis (Geissler, W.M. et al. (1994) Nat. Genet. 7:34-39). An excess of androgens such as DHTT can contribute to certain disease states such as benign prostatic hyperplasia and prostate cancer.

Oxidoreductases are components of the fatty acid metabolism pathways in mitochondria and peroxisomes. The main beta-oxidation pathway degrades both saturated and unsaturated fatty acids, while the auxiliary pathway performs additional steps required for the degradation of unsaturated fatty acids. The auxiliary beta-oxidation enzyme 2,4-dienoyl-CoA reductase catalyzes the removal of even-numbered double bonds from unsaturated fatty acids prior to their entry into the main beta-oxidation pathway. The enzyme may also remove odd-numbered double bonds from unsaturated fatty acids (Koivuranta, K.T. et al. (1994) Biochem. J. 304:787-792; Smeland, T.E. et al. (1992) Proc. Natl. Acad. Sci. USA 89:6673-6677). 2,4-dienoyl-CoA reductase is located in both mitochondria and

peroxisomes. Inherited deficiencies in mitochondrial and peroxisomal beta-oxidation enzymes are associated with severe diseases, some of which manifest themselves soon after birth and lead to death within a few years. Defects in beta-oxidation are associated with Reye's syndrome, Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum's disease, acyl-CoA oxidase deficiency, and bifunctional protein deficiency (Suzuki, Y. et al. (1994) Am. J. Hum. Genet. 54:36-43; Hoefler, supra; Cotran, R.S. et al. (1994) Robbins Pathologic Basis of Disease, W.B. Saunders Co., Philadelphia PA, p.866). Peroxisomal beta-oxidation is impaired in cancerous tissue. Although neoplastic human breast epithelial cells have the same number of peroxisomes as do normal cells, fatty acyl-CoA oxidase activity is lower than in control tissue (el Bouhtoury, F. et al. (1992) J. Pathol. 166:27-35). Human colon carcinomas have fewer peroxisomes than normal colon tissue and have lower fatty-acyl-CoA oxidase and bifunctional enzyme (including enoyl-CoA hydratase) activities than normal tissue (Cable, S. et al. (1992) Virchows Arch. B Cell Pathol. Incl. Mol. Pathol. 62:221-226). Another important oxidoreductase is isocitrate dehydrogenase, which catalyzes the conversion of isocitrate to a-ketoglutarate, a substrate of the citric acid cycle. Isocitrate dehydrogenase can be either NAD or NADP dependent, and is found in the cytosol, mitochondria, and peroxisomes. Activity of isocitrate dehydrogenase is regulated developmentally, and by hormones, neurotransmitters, and growth factors.

Hydroxypyruvate reductase (HPR), a peroxisomal 2-hydroxyacid dehydrogenase in the glycolate pathway, catalyzes the conversion of hydroxypyruvate to glycerate with the oxidation of both NADH and NADPH. The reverse dehydrogenase reaction reduces NAD^+ and $NADP^+$. HPR recycles nucleotides and bases back into pathways leading to the synthesis of ATP and GTP. ATP and GTP are used to produce DNA and RNA and to control various aspects of signal transduction and energy metabolism. Inhibitors of purine nucleotide biosynthesis have long been employed as antiproliferative agents to treat cancer and viral diseases. HPR also regulates biochemical synthesis of serine and cellular serine levels available for protein synthesis.

The mitochondrial electron transport (or respiratory) chain is a series of oxidoreductase-type enzyme complexes in the mitochondrial membrane that is responsible for the transport of electrons from NADH through a series of redox centers within these complexes to oxygen, and the coupling of this oxidation to the synthesis of ATP (oxidative phosphorylation). ATP then provides the primary source of energy for driving a cell's many energy-requiring reactions. The key complexes in the respiratory chain are NADH:ubiquinone oxidoreductase (complex I), succinate:ubiquinone oxidoreductase (complex II), cytochrome c_1-b oxidoreductase (complex III), cytochrome c oxidase (complex IV), and ATP synthase (complex V) (Alberts, B. et al. (1994) Molecular Biology of the Cell, Garland Publishing, Inc., New York NY, pp. 677-678). All of these complexes are located on the inner matrix side of the mitochondrial membrane except complex II, which is on the cytosolic

side. Complex II transports electrons generated in the citric acid cycle to the respiratory chain. The electrons generated by oxidation of succinate to fumarate in the citric acid cycle are transferred through electron carriers in complex II to membrane bound ubiquinone (Q). Transcriptional regulation of these nuclear-encoded genes appears to be the predominant means for controlling the biogenesis of respiratory enzymes. Defects and altered expression of enzymes in the respiratory chain are associated with a variety of disease conditions.

Other dehydrogenase activities using NAD as a cofactor are also important in mitochondrial function. 3-hydroxyisobutyrate dehydrogenase (3HBD), important in valine catabolism, catalyzes the NAD-dependent oxidation of 3-hydroxyisobutyrate to methylmalonate semialdehyde within mitochondria. Elevated levels of 3-hydroxyisobutyrate have been reported in a number of disease states, including ketoacidosis, methylmalonic acidemia, and other disorders associated with deficiencies in methylmalonate semialdehyde dehydrogenase (Rougraff, P.M. et al. (1989) J. Biol. Chem. 264:5899-5903).

Another mitochondrial dehydrogenase important in amino acid metabolism is the enzyme isovaleryl-CoA-dehydrogenase (IVD). IVD is involved in leucine metabolism and catalyzes the oxidation of isovaleryl-CoA to 3-methylcrotonyl-CoA. Human IVD is a tetrameric flavoprotein that is encoded in the nucleus and synthesized in the cytosol as a 45 kDa precursor with a mitochondrial import signal sequence. A genetic deficiency, caused by a mutation in the gene encoding IVD, results in the condition known as isovaleric acidemia. This mutation results in inefficient mitochondrial import and processing of the IVD precursor (Vockley, J. et al. (1992) J. Biol. Chem. 267:2494-2501).

Transferases

Transferases are enzymes that catalyze the transfer of molecular groups. The reaction may involve an oxidation, reduction, or cleavage of covalent bonds, and is often specific to a substrate or to particular sites on a type of substrate. Transferases participate in reactions essential to such functions as synthesis and degradation of cell components, regulation of cell functions including cell signaling, cell proliferation, inflamation, apoptosis, secretion and excretion. Transferases are involved in key steps in disease processes involving these functions. Transferases are frequently classified according to the type of group transferred. For example, methyl transferases transfer one-carbon methyl groups, amino transferases transfer nitrogenous amino groups, and similarly denominated enzymes transfer aldehyde or ketone, acyl, glycosyl, alkyl or aryl, isoprenyl, saccharyl, phosphorous-containing, sulfur-containing, or selenium-containing groups, as well as small enzymatic groups such as Coenzyme A.

Acyl transferases include peroxisomal carnitine octanoyl transferase, which is involved in the fatty acid beta-oxidation pathway, and mitochondrial carnitine palmitoyl transferases, involved in fatty acid metabolism and transport. Choline O-acetyl transferase catalyzes the biosynthesis of the

neurotransmitter acetylcholine.

Amino transferases play key roles in protein synthesis and degradation, and they contribute to other processes as well. For example, the amino transferase 5-aminolevulinic acid synthase catalyzes the addition of succinyl-CoA to glycine, the first step in heme biosynthesis. Other amino transferases participate in pathways important for neurological function and metabolism. For example, glutamine-phenylpyruvate amino transferase, also known as glutamine transaminase K (GTK), catalyzes several reactions with a pyridoxal phosphate cofactor. GTK catalyzes the reversible conversion of L-glutamine and phenylpyruvate to 2-oxoglutaramate and L-phenylalanine. Other amino acid substrates for GTK include L-methionine, L-histidine, and L-tyrosine. GTK also catalyzes the conversion of kynurenine to kynurenic acid, a tryptophan metabolite that is an antagonist of the N-methyl-D-aspartate (NMDA) receptor in the brain and may exert a neuromodulatory function. Alteration of the kynurenine metabolic pathway may be associated with several neurological disorders. GTK also plays a role in the metabolism of halogenated xenobiotics conjugated to glutathione, leading to nephrotoxicity in rats and neurotoxicity in humans. GTK is expressed in kidney, liver, and brain. Both human and rat GTKs contain a putative pyridoxal phosphate binding site (ExPASy ENZYME: EC 2.6.1.64; Perry, S.J. et al. (1993) Mol. Pharmacol. 43:660-665; Perry, S. et al. (1995) FEBS Lett. 360:277-280; and Alberati-Giani, D. et al. (1995) J. Neurochem. 64:1448-1455). A second amino transferase associated with this pathway is kynurenine/α-aminoadipate amino transferase (AadAT). AadAT catalyzes the reversible conversion of α-aminoadipate and α-ketoglutarate to α-ketoadipate and L-glutamate during lysine metabolism. AadAT also catalyzes the transamination of kynurenine to kynurenic acid. A cytosolic AadAT is expressed in rat kidney, liver, and brain (Nakatani, Y. et al. (1970) Biochim. Biophys. Acta 198:219-228; Buchli, R. et al. (1995) J. Biol. Chem. 270:29330-29335).

Glycosyl transferases include the mammalian UDP-glucouronosyl transferases, a family of membrane-bound microsomal enzymes catalyzing the transfer of glucouronic acid to lipophilic substrates in reactions that play important roles in detoxification and excretion of drugs, carcinogens, and other foreign substances. Another mammalian glycosyl transferase, mammalian UDP-galactose-ceramide galactosyl transferase, catalyzes the transfer of galactose to ceramide in the synthesis of galactocerebrosides in myelin membranes of the nervous system. The UDP-glycosyl transferases share a conserved signature domain of about 50 amino acid residues (PROSITE: PDOC00359, http://expasy.hcuge.ch/sprot/prosite.html).

Methyl transferases are involved in a variety of pharmacologically important processes. Nicotinamide N-methyl transferase catalyzes the N-methylation of nicotinamides and other pyridines, an important step in the cellular handling of drugs and other foreign compounds.
Phenylethanolamine N-methyl transferase catalyzes the conversion of noradrenalin to adrenalin. 6-O-

methylguanine-DNA methyl transferase reverses DNA methylation, an important step in carcinogenesis. Uroporphyrin-III C-methyl transferase, which catalyzes the transfer of two methyl groups from S-adenosyl-L-methionine to uroporphyrinogen III, is the first specific enzyme in the biosynthesis of cobalamin, a dietary enzyme whose uptake is deficient in pernicious anemia. Protein-arginine methyl transferases catalyze the posttranslational methylation of arginine residues in proteins, resulting in the mono- and dimethylation of arginine on the guanidino group. Substrates include histones, myelin basic protein, and heterogeneous nuclear ribonucleoproteins involved in mRNA processing, splicing, and transport. Protein-arginine methyl transferase interacts with proteins upregulated by mitogens, with proteins involved in chronic lymphocytic leukemia, and with interferon, suggesting an important role for methylation in cytokine receptor signaling (Lin, W.-J. et al. (1996) J. Biol. Chem. 271:15034-15044; Abramovich, C. et al. (1997) EMBO J. 16:260-266; and Scott, H.S. et al. (1998) Genomics 48:330-340).

Phosphotransferases catalyze the transfer of high-energy phosphate groups and are important in energy-requiring and -releasing reactions. The metabolic enzyme creatine kinase catalyzes the reversible phosphate transfer between creatine/creatine phosphate and ATP/ADP. Glycocyamine kinase catalyzes phosphate transfer from ATP to guanidoacetate, and arginine kinase catalyzes phosphate transfer from ATP to arginine. A cysteine-containing active site is conserved in this family (PROSITE: PDOC00103).

Prenyl transferases are heterodimers, consisting of an alpha and a beta subunit, that catalyze the transfer of an isoprenyl group. An example of a prenyl transferase is the mammalian protein farnesyl transferase. The alpha subunit of farnesyl transferase consists of 5 repeats of 34 amino acids each, with each repeat containing an invariant tryptophan (PROSITE: PDOC00703).

Saccharyl transferases are glycating enzymes involved in a variety of metabolic processes. Oligosacchryl transferase-48, for example, is a receptor for advanced glycation endproducts. Accumulation of these endproducts is observed in vascular complications of diabetes, macrovascular disease, renal insufficiency, and Alzheimer's disease (Thornalley, P.J. (1998) Cell Mol. Biol. (Noisy-Le-Grand) 44:1013-1023).

Coenzyme A (CoA) transferase catalyzes the transfer of CoA between two carboxylic acids. Succinyl CoA:3-oxoacid CoA transferase, for example, transfers CoA from succinyl-CoA to a recipient such as acetoacetate. Acetoacetate is essential to the metabolism of ketone bodies, which accumulate in tissues affected by metabolic disorders such as diabetes (PROSITE: PDOC00980).

<u>Hydrolases</u>

Hydrolysis is the breaking of a covalent bond in a substrate by introduction of a molecule of water. The reaction involves a nucleophilic attack by the water molecule's oxygen atom on a target bond in the substrate. The water molecule is split across the target bond, breaking the bond and

generating two product molecules. Hydrolases participate in reactions essential to such functions as synthesis and degradation of cell components, and for regulation of cell functions including cell signaling, cell proliferation, inflamation, apoptosis, secretion and excretion. Hydrolases are involved in key steps in disease processes involving these functions. Hydrolytic enzymes, or hydrolases, may be grouped by substrate specificity into classes including phosphatases, peptidases, lysophospholipases, phosphodiesterases, glycosidases, and glyoxalases.

Phosphatases hydrolytically remove phosphate groups from proteins, an energy-providing step that regulates many cellular processes, including intracellular signaling pathways that in turn control cell growth and differentiation, cell-cell contact, the cell cycle, and oncogenesis.

Lysophospholipases (LPLs) regulate intracellular lipids by catalyzing the hydrolysis of ester bonds to remove an acyl group, a key step in lipid degradation. Small LPL isoforms, approximately 15-30 kD, function as hydrolases; larger isoforms function both as hydrolases and transacylases. A particular substrate for LPLs, lysophosphatidylcholine, causes lysis of cell membranes. LPL activity is regulated by signaling molecules important in numerous pathways, including the inflammatory response.

Peptidases, also called proteases, cleave peptide bonds that form the backbone of peptide or protein chains. Proteolytic processing is essential to cell growth, differentiation, remodeling, and homeostasis as well as inflammation and immune response. Since typical protein half-lives range from hours to a few days, peptidases are continually cleaving precursor proteins to their active form, removing signal sequences from targeted proteins, and degrading aged or defective proteins. Peptidases function in bacterial, parasitic, and viral invasion and replication within a host. Examples of peptidases include trypsin and chymotrypsin (components of the complement cascade and the blood-clotting cascade) lysosomal cathepsins, calpains, pepsin, renin, and chymosin (Beynon, R.J. and J.S. Bond (1994) Proteolytic Enzymes: A Practical Approach, Oxford University Press, New York NY, pp. 1-5).

The phosphodiesterases catalyze the hydrolysis of one of the two ester bonds in a phosphodiester compound. Phosphodiesterases are therefore crucial to a variety of cellular processes. Phosphodiesterases include DNA and RNA endo- and exo-nucleases, which are essential to cell growth and replication as well as protein synthesis. Another phosphodiesterase is acid sphingomyelinase, which hydrolyzes the membrane phospholipid sphingomyelin to ceramide and phosphorylcholine. Phosphorylcholine is used in the synthesis of phosphatidylcholine, which is involved in numerous intracellular signaling pathways. Ceramide is an essential precursor for the generation of gangliosides, membrane lipids found in high concentration in neural tissue. Defective acid sphingomyelinase phosphodiesterase leads to a build-up of sphingomyelin molecules in lysosomes, resulting in Niemann-Pick disease.

Glycosidases catalyze the cleavage of hemiacetyl bonds of glycosides, which are compounds that contain one or more sugar. Mammalian lactase-phlorizin hydrolase, for example, is an intestinal enzyme that splits lactose. Mammalian beta-galactosidase removes the terminal galactose from gangliosides, glycoproteins, and glycosaminoglycans, and deficiency of this enzyme is associated with a gangliosidosis known as Morquio disease type B. Vertebrate lysosomal alpha-glucosidase, which hydrolyzes glycogen, maltose, and isomaltose, and vertebrate intestinal sucrase-isomaltase, which hydrolyzes sucrose, maltose, and isomaltose, are widely distributed members of this family with highly conserved sequences at their active sites.

The glyoxylase system is involved in gluconeogenesis, the production of glucose from storage compounds in the body. It consists of glyoxylase I, which catalyzes the formation of S-D-lactoylglutathione from methyglyoxal, a side product of triose-phosphate energy metabolism, and glyoxylase II, which hydrolyzes S-D-lactoylglutathione to D-lactic acid and reduced glutathione. Glyoxylases are involved in hyperglycemia, non-insulin-dependent diabetes mellitus, the detoxification of bacterial toxins, and in the control of cell proliferation and microtubule assembly.

Lyases

Lyases are a class of enzymes that catalyze the cleavage of C-C, C-O, C-N, C-S, C-(halide), P-O or other bonds without hydrolysis or oxidation to form two molecules, at least one of which contains a double bond (Stryer, L. (1995) Biochemistry W.H. Freeman and Co. New York, NY p.620). Lyases are critical components of cellular biochemistry with roles in metabolic energy production including fatty acid metabolism, as well as other diverse enzymatic processes. Further classification of lyases reflects the type of bond cleaved as well as the nature of the cleaved group.

The group of C-C lyases include carboxyl-lyases (decarboxylases), aldehyde-lyases (aldolases), oxo-acid-lyases and others. The C-O lyase group includes hydro-lyases, lyases acting on polysaccharides and other lyases. The C-N lyase group includes ammonia-lyases, amidine-lyases, amine-lyases (deaminases) and other lyases.

Proper regulation of lyases is critical to normal physiology. For example, mutation induced deficiencies in the uroporphyrinogen decarboxylase can lead to photosensitive cutaneous lesions in the genetically-linked disorder familial porphyria cutanea tarda (Mendez, M. et al. (1998) Am. J. Genet. 63:1363-1375). It has also been shown that adenosine deaminase (ADA) deficiency stems from genetic mutations in the ADA gene, resulting in the disorder severe combined immunodeficiency disease (SCID) (Hershfield, M.S. (1998) Semin. Hematol. 35:291-298).

Isomerases

Isomerases are a class of enzymes that catalyze geometric or structural changes within a molecule to form a single product. This class includes racemases and epimerases, cis-trans-isomerases, intramolecular oxidoreductases, intramolecular transferases (mutases) and intramolecular

lyases. Isomerases are critical components of cellular biochemistry with roles in metabolic energy production including glycolysis, as well as other diverse enzymatic processes (Stryer, L. (1995) Biochemistry, W.H. Freeman and Co., New York NY, pp.483-507).

Racemases are a subset of isomerases that catalyze inversion of a molecules configuration around the asymmetric carbon atom in a substrate having a single center of asymmetry, thereby interconverting two racemers. Epimerases are another subset of isomerases that catalyze inversion of configuration around an asymmetric carbon atom in a substrate with more than one center of symmetry, thereby interconverting two epimers. Racemases and epimerases can act on amino acids and derivatives, hydroxy acids and derivatives, as well as carbohydrates and derivatives. The interconversion of UDP-galactose and UDP-glucose is catalyzed by UDP-galactose-4'-epimerase. Proper regulation and function of this epimerase is essential to the synthesis of glycoproteins and glycolipids. Elevated blood galactose levels have been correlated with UDP-galactose-4'-epimerase deficiency in screening programs of infants (Gitzelmann, R. (1972) Helv. Paediat. Acta 27:125-130).

Oxidoreductases can be isomerases as well. Oxidoreductases catalyze the reversible transfer of electrons from a substrate that becomes oxidized to a substrate that becomes reduced. This class of enzymes includes dehydrogenases, hydroxylases, oxidases, oxygenases, peroxidases, and reductases. Proper maintenance of oxidoreductase levels is physiologically important. For example, genetically-linked deficiencies in lipoamide dehydrogenase can result in lactic acidosis (Robinson, B.H. et al. (1977) Pediat. Res. 11:1198-1202).

Another subgroup of isomerases are the transferases (or mutases). Transferases transfer a chemical group from one compound (the donor) to another compound (the acceptor). The types of groups transferred by these enzymes include acyl groups, amino groups, phosphate groups (phosphotransferases or phosphomutases), and others. The transferase carnitine palmitoyltransferase is an important component of fatty acid metabolism. Genetically-linked deficiencies in this transferase can lead to myopathy (Scriver, C.R. et al. (1995) The Metabolic and Molecular Basis of Inherited Disease, McGraw-Hill, New York NY, pp.1501-1533).

Yet another subgroup of isomerases are the topoisomersases. Topoisomerases are enzymes that affect the topological state of DNA. For example, defects in topoisomerases or their regulation can affect normal physiology. Reduced levels of topoisomerase II have been correlated with some of the DNA processing defects associated with the disorder ataxia-telangiectasia (Singh, S.P. et al. (1988) Nucleic Acids Res. 16:3919-3929).

Ligases

Ligases catalyze the formation of a bond between two substrate molecules. The process involves the hydrolysis of a pyrophosphate bond in ATP or a similar energy donor. Ligases are classified based on the nature of the type of bond they form, which can include carbon-oxygen,

carbon-sulfur, carbon-nitrogen, carbon-carbon and phosphoric ester bonds.

Ligases forming carbon-oxygen bonds include the aminoacyl-transfer RNA (tRNA) synthetases which are important RNA-associated enzymes with roles in translation. Protein biosynthesis depends on each amino acid forming a linkage with the appropriate tRNA. The aminoacyl-tRNA synthetases are responsible for the activation and correct attachment of an amino acid with its cognate tRNA. The 20 aminoacyl-tRNA synthetase enzymes can be divided into two structural classes, and each class is characterized by a distinctive topology of the catalytic domain. Class I enzymes contain a catalytic domain based on the nucleotide-binding Rossman fold. Class II enzymes contain a central catalytic domain, which consists of a seven-stranded antiparallel ß-sheet motif, as well as N- and C- terminal regulatory domains. Class II enzymes are separated into two groups based on the heterodimeric or homodimeric structure of the enzyme; the latter group is further subdivided by the structure of the N- and C-terminal regulatory domains (Hartlein, M. and S. Cusack (1995) J. Mol. Evol. 40:519-530). Autoantibodies against aminoacyl-tRNAs are generated by patients with dermatomyositis and polymyositis, and correlate strongly with complicating interstitial lung disease (ILD). These antibodies appear to be generated in response to viral infection, and coxsackie virus has been used to induce experimental viral myositis in animals.

Ligases forming carbon-sulfur bonds (Acid-thiol ligases) mediate a large number of cellular biosynthetic intermediary metabolism processes involve intermolecular transfer of carbon atom-containing substrates (carbon substrates). Examples of such reactions include the tricarboxylic acid cycle, synthesis of fatty acids and long-chain phospholipids, synthesis of alcohols and aldehydes, synthesis of intermediary metabolites, and reactions involved in the amino acid degradation pathways. Some of these reactions require input of energy, usually in the form of conversion of ATP to either ADP or AMP and pyrophosphate.

In many cases, a carbon substrate is derived from a small molecule containing at least two carbon atoms. The carbon substrate is often covalently bound to a larger molecule which acts as a carbon substrate carrier molecule within the cell. In the biosynthetic mechanisms described above, the carrier molecule is coenzyme A. Coenzyme A (CoA) is structurally related to derivatives of the nucleotide ADP and consists of 4'-phosphopantetheine linked via a phosphodiester bond to the alpha phosphate group of adenosine 3',5'-bisphosphate. The terminal thiol group of 4'-phosphopantetheine acts as the site for carbon substrate bond formation. The predominant carbon substrates which utilize CoA as a carrier molecule during biosynthesis and intermediary metabolism in the cell are acetyl, succinyl, and propionyl moieties, collectively referred to as acyl groups. Other carbon substrates include enoyl lipid, which acts as a fatty acid oxidation intermediate, and carnitine, which acts as an acetyl-CoA flux regulator/ mitochondrial acyl group transfer protein. Acyl-CoA and acetyl-CoA are synthesized in the cell by acyl-CoA synthetase and acetyl-CoA synthetase, respectively.

Activation of fatty acids is mediated by at least three forms of acyl-CoA synthetase activity: i) acetyl-CoA synthetase, which activates acetate and several other low molecular weight carboxylic acids and is found in muscle mitochondria and the cytosol of other tissues; ii) medium-chain acyl-CoA synthetase, which activates fatty acids containing between four and eleven carbon atoms (predominantly from dietary sources), and is present only in liver mitochondria; and iii) acyl CoA synthetase, which is specific for long chain fatty acids with between six and twenty carbon atoms, and is found in microsomes and the mitochondria. Proteins associated with acyl-CoA synthetase activity have been identified from many sources including bacteria, yeast, plants, mouse, and man. The activity of acyl-CoA synthetase may be modulated by phosphorylation of the enzyme by cAMP-dependent protein kinase.

Ligases forming carbon-nitrogen bonds include amide synthases such as glutamine synthetase (glutamate-ammonia ligase) that catalyzes the amination of glutamic acid to glutamine by ammonia using the energy of ATP hydrolysis. Glutamine is the primary source for the amino group in various amide transfer reactions involved in de novo pyrimidine nucleotide synthesis and in purine and pyrimidine ribonucleotide interconversions. Overexpression of glutamine synthetase has been observed in primary liver cancer (Christa, L. et al. (1994) Gastroent. 106:1312-1320).

Acid-amino-acid ligases (peptide synthases) are represented by the ubiquitin proteases which are associated with the ubiquitin conjugation system (UCS), a major pathway for the degradation of cellular proteins in eukaryotic cells and some bacteria. The UCS mediates the elimination of abnormal proteins and regulates the half-lives of important regulatory proteins that control cellular processes such as gene transcription and cell cycle progression. In the UCS pathway, proteins targeted for degradation are conjugated to a ubiquitin (Ub), a small heat stable protein. Ub is first activated by a ubiquitin-activating enzyme (E1), and then transferred to one of several Ub-conjugating enzymes (E2). E2 then links the Ub molecule through its C-terminal glycine to an internal lysine (acceptor lysine) of a target protein. The ubiquitinated protein is then recognized and degraded by proteasome, a large, multisubunit proteolytic enzyme complex, and ubiquitin is released for reutilization by ubiquitin protease. The UCS is implicated in the degradation of mitotic cyclic kinases, oncoproteins, tumor suppressor genes such as p53, viral proteins, cell surface receptors associated with signal transduction, transcriptional regulators, and mutated or damaged proteins (Ciechanover, A. (1994) Cell 79:13-21). A murine proto-oncogene, Unp, encodes a nuclear ubiquitin protease whose overexpression leads to oncogenic transformation of NIH3T3 cells, and the human homolog of this gene is consistently elevated in small cell tumors and adenocarcinomas of the lung (Gray, D.A. (1995) Oncogene 10:2179-2183).

Cyclo-ligases and other carbon-nitrogen ligases comprise various enzymes and enzyme complexes that participate in the de novo pathways to purine and pyrimidine biosynthesis. Because

these pathways are critical to the synthesis of nucleotides for replication of both RNA and DNA, many of these enzymes have been the targets of clinical agents for the treatment of cell proliferative disorders such as cancer and infectious diseases.

Purine biosynthesis occurs de novo from the amino acids glycine and glutamine, and other small molecules. Three of the key reactions in this process are catalyzed by a trifunctional enzyme composed of glycinamide-ribonucleotide synthetase (GARS), aminoimidazole ribonucleotide synthetase (AIRS), and glycinamide ribonucleotide transformylase (GART). Together these three enzymes combine ribosylamine phosphate with glycine to yield phosphoribosyl aminoimidazole, a precursor to both adenylate and guanylate nucleotides. This trifunctional protein has been implicated in the pathology of Downs syndrome (Aimi, J. et al. (1990) Nucleic Acid Res. 18:6665-6672). Adenylosuccinate synthetase catalyzes a later step in purine biosynthesis that converts inosinic acid to adenylosuccinate, a key step on the path to ATP synthesis. This enzyme is also similar to another carbon-nitrogen ligase, argininosuccinate synthetase, that catalyzes a similar reaction in the urea cycle (Powell, S.M. et al. (1992) FEBS Lett. 303:4-10).

Like the de novo biosynthesis of purines, de novo synthesis of the pyrimidine nucleotides uridylate and cytidylate also arises from a common precursor, in this instance the nucleotide orotidylate derived from orotate and phosphoribosyl pyrophosphate (PPRP). Again a trifunctional enzyme comprising three carbon-nitrogen ligases plays a key role in the process. In this case the enzymes aspartate transcarbamylase (ATCase), carbamyl phosphate synthetase II, and dihydroorotase (DHOase) are encoded by a single gene called CAD. Together these three enzymes combine the initial reactants in pyrimidine biosynthesis, glutamine, CO_2 and ATP to form dihydroorotate, the precursor to orotate and orotidylate (Iwahana, H. et al. (1996) Biochem. Biophys. Res. Commun. 219:249-255). Further steps then lead to the synthesis of uridine nucleotides from orotidylate. Cytidine nucleotides are derived from uridine-5'-triphosphate (UTP) by the amidation of UTP using glutamine as the amino donor and the enzyme CTP synthetase. Regulatory mutations in the human CTP synthetase are believed to confer multi-drug resistance to agents widely used in cancer therapy (Yamauchi, M. et al. (1990) EMBO J. 9:2095-2099).

Ligases forming carbon-carbon bonds include the carboxylases acetyl-CoA carboxylase and pyruvate carboxylase. Acetyl-CoA carboxylase catalyzes the carboxylation of acetyl-CoA from CO_2 and H_2O using the energy of ATP hydrolysis. Acetyl-CoA carboxylase is the rate-limiting step in the biogenesis of long-chain fatty acids. Two isoforms of acetyl-CoA carboxylase, types I and types II, are expressed in human in a tissue-specific manner (Ha, J. et al. (1994) Eur. J. Biochem. 219:297-306). Pyruvate carboxylase is a nuclear-encoded mitochondrial enzyme that catalyzes the conversion of pyruvate to oxaloacetate, a key intermediate in the citric acid cycle.

Ligases forming phosphoric ester bonds include the DNA ligases involved in both DNA

replication and repair. DNA ligases seal phosphodiester bonds between two adjacent nucleotides in a DNA chain using the energy from ATP hydrolysis to first activate the free 5'-phosphate of one nucleotide and then react it with the 3'-OH group of the adjacent nucleotide. This resealing reaction is used in both DNA replication to join small DNA fragments called Okazaki fragments that are transiently formed in the process of replicating new DNA, and in DNA repair. DNA repair is the process by which accidental base changes, such as those produced by oxidative damage, hydrolytic attack, or uncontrolled methylation of DNA, are corrected before replication or transcription of the DNA can occur. Bloom's syndrome is an inherited human disease in which individuals are partially deficient in DNA ligation and consequently have an increased incidence of cancer (Alberts, B. et al. (1994) The Molecular Biology of the Cell, Garland Publishing Inc., New York NY, p. 247).

Molecules Associated with Growth and Development

SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71 encode, for example, molecules associated with growth and development.

Human growth and development requires the spatial and temporal regulation of cell differentiation, cell proliferation, and apoptosis. These processes coordinately control reproduction, aging, embryogenesis, morphogenesis, organogenesis, and tissue repair and maintenance. At the cellular level, growth and development is governed by the cell's decision to enter into or exit from the cell division cycle and by the cell's commitment to a terminally differentiated state. These decisions are made by the cell in response to extracellular signals and other environmental cues it receives. The following discussion focuses on the molecular mechanisms of cell division, reproduction, cell differentiation and proliferation, apoptosis, and aging.

Cell Division

Cell division is the fundamental process by which all living things grow and reproduce. In unicellular organisms such as yeast and bacteria, each cell division doubles the number of organisms, while in multicellular species many rounds of cell division are required to replace cells lost by wear or by programmed cell death, and for cell differentiation to produce a new tissue or organ. Details of the cell division cycle may vary, but the basic process consists of three principle events. The first event, interphase, involves preparations for cell division, replication of the DNA, and production of essential proteins. In the second event, mitosis, the nuclear material is divided and separates to opposite sides of the cell. The final event, cytokinesis, is division and fission of the cell cytoplasm. The sequence and timing of cell cycle transitions is under the control of the cell cycle regulation system which controls the process by positive or negative regulatory circuits at various check points.

Regulated progression of the cell cycle depends on the integration of growth control pathways

with the basic cell cycle machinery. Cell cycle regulators have been identified by selecting for human and yeast cDNAs that block or activate cell cycle arrest signals in the yeast mating pheromone pathway when they are overexpressed. Known regulators include human CPR (cell cycle progression restoration) genes, such as CPR8 and CPR2, and yeast CDC (cell division control) genes, including CDC91, that block the arrest signals. The CPR genes express a variety of proteins including cyclins, tumor suppressor binding proteins, chaperones, transcription factors, translation factors, and RNA-binding proteins (Edwards, M.C. et al.(1997) Genetics 147:1063-1076).

Several cell cycle transitions, including the entry and exit of a cell from mitosis, are dependent upon the activation and inhibition of cyclin-dependent kinases (Cdks). The Cdks are composed of a kinase subunit, Cdk, and an activating subunit, cyclin, in a complex that is subject to many levels of regulation. There appears to be a single Cdk in Saccharomyces cerevisiae and Saccharomyces pombe whereas mammals have a variety of specialized Cdks. Cyclins act by binding to and activating cyclin-dependent protein kinases which then phosphorylate and activate selected proteins involved in the mitotic process. The Cdk-cyclin complex is both positively and negatively regulated by phosphorylation, and by targeted degradation involving molecules such as CDC4 and CDC53. In addition, Cdks are further regulated by binding to inhibitors and other proteins such as Suc1 that modify their specificity or accessibility to regulators (Patra, D. and W.G. Dunphy (1996) Genes Dev. 10:1503-1515; and Mathias, N. et al. (1996) Mol. Cell Biol. 16:6634-6643).

Reproduction

The male and female reproductive systems are complex and involve many aspects of growth and development. The anatomy and physiology of the male and female reproductive systems are reviewed in (Guyton, A.C. (1991) Textbook of Medical Physiology, W.B. Saunders Co., Philadelphia PA, pp. 899-928).

The male reproductive system includes the process of spermatogenesis, in which the sperm are formed, and male reproductive functions are regulated by various hormones and their effects on accessory sexual organs, cellular metabolism, growth, and other bodily functions.

Spermatogenesis begins at puberty as a result of stimulation by gonadotropic hormones released from the anterior pituitary. Immature sperm (spermatogonia) undergo several mitotic cell divisions before undergoing meiosis and full maturation. The testes secrete several male sex hormones, the most abundant being testosterone, that is essential for growth and division of the immature sperm, and for the masculine characteristics of the male body. Three other male sex hormones, gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) control sexual function.

The uterus, ovaries, fallopian tubes, vagina, and breasts comprise the female reproductive

system. The ovaries and uterus are the source of ova and the location of fetal development, respectively. The fallopian tubes and vagina are accessory organs attached to the top and bottom of the uterus, respectively. Both the uterus and ovaries have additional roles in the development and loss of reproductive capability during a female's lifetime. The primary role of the breasts is lactation. Multiple endocrine signals from the ovaries, uterus, pituitary, hypothalamus, adrenal glands, and other tissues coordinate reproduction and lactation. These signals vary during the monthly menstruation cycle and during the female's lifetime. Similarly, the sensitivity of reproductive organs to these endocrine signals varies during the female's lifetime.

A combination of positive and negative feedback to the ovaries, pituitary and hypothalamus glands controls physiologic changes during the monthly ovulation and endometrial cycles. The anterior pituitary secretes two major gonadotropin hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), regulated by negative feedback of steroids, most notably by ovarian estradiol. If fertilization does not occur, estrogen and progesterone levels decrease. This sudden reduction of the ovarian hormones leads to menstruation, the desquamation of the endometrium.

Hormones further govern all the steps of pregnancy, parturition, lactation, and menopause. During pregnancy large quantities of human chorionic gonadotropin (hCG), estrogens, progesterone, and human chorionic somatomammotropin (hCS) are formed by the placenta. hCG, a glycoprotein similar to luteinizing hormone, stimulates the corpus luteum to continue producing more progesterone and estrogens, rather than to involute as occurs if the ovum is not fertilized. hCS is similar to growth hormone and is crucial for fetal nutrition.

The female breast also matures during pregnancy. Large amounts of estrogen secreted by the placenta trigger growth and branching of the breast milk ductal system while lactation is initiated by the secretion of prolactin by the pituitary gland.

Parturition involves several hormonal changes that increase uterine contractility toward the end of pregnancy, as follows. The levels of estrogens increase more than those of progesterone. Oxytocin is secreted by the neurohypophysis. Concomitantly, uterine sensitivity to oxytocin increases. The fetus itself secretes oxytocin, cortisol (from adrenal glands), and prostaglandins.

Menopause occurs when most of the ovarian follicles have degenerated. The ovary then produces less estradiol, reducing the negative feedback on the pituitary and hypothalamus glands. Mean levels of circulating FSH and LH increase, even as ovulatory cycles continue. Therefore, the ovary is less responsive to gonadotropins, and there is an increase in the time between menstrual cycles. Consequently, menstrual bleeding ceases and reproductive capability ends.

Cell Differentiation and Proliferation

Tissue growth involves complex and ordered patterns of cell proliferation, cell differentiation,

and apoptosis. Cell proliferation must be regulated to maintain both the number of cells and their spatial organization. This regulation depends upon the appropriate expression of proteins which control cell cycle progression in response to extracellular signals, such as growth factors and other mitogens, and intracellular cues, such as DNA damage or nutrient starvation. Molecules which directly or indirectly modulate cell cycle progression fall into several categories, including growth factors and their receptors, second messenger and signal transduction proteins, oncogene products, tumor-suppressor proteins, and mitosis-promoting factors.

Growth factors were originally described as serum factors required to promote cell proliferation. Most growth factors are large, secreted polypeptides that act on cells in their local environment. Growth factors bind to and activate specific cell surface receptors and initiate intracellular signal transduction cascades. Many growth factor receptors are classified as receptor tyrosine kinases which undergo autophosphorylation upon ligand binding. Autophosphorylation enables the receptor to interact with signal transduction proteins characterized by the presence of SH2 or SH3 domains (Src homology regions 2 or 3). These proteins then modulate the activity state of small G-proteins, such as Ras, Rab, and Rho, along with GTPase activating proteins (GAPs), guanine nucleotide releasing proteins (GNRPs), and other guanine nucleotide exchange factors. Small G proteins act as molecular switches that activate other downstream events, such as mitogen-activated protein kinase (MAP kinase) cascades. MAP kinases ultimately activate transcription of mitosis-promoting genes.

In addition to growth factors, small signaling peptides and hormones also influence cell proliferation. These molecules bind primarily to another class of receptor, the trimeric G-protein coupled receptor (GPCR), found predominantly on the surface of immune, neuronal and neuroendocrine cells. Upon ligand binding, the GPCR activates a trimeric G protein which in turn triggers increased levels of intracellular second messengers such as phospholipase C, Ca2+, and cyclic AMP. Most GPCR-mediated signaling pathways indirectly promote cell proliferation by causing the secretion or breakdown of other signaling molecules that have direct mitogenic effects. These signaling cascades often involve activation of kinases and phosphatases. Some growth factors, such as some members of the transforming growth factor beta (TGF-β) family, act on some cells to stimulate cell proliferation and on other cells to inhibit it. Growth factors may also stimulate a cell at one concentration and inhibit the same cell at another concentration. Most growth factors also have a multitude of other actions besides the regulation of cell growth and division: they can control the proliferation, survival, differentiation, migration, or function of cells depending on the circumstance. For example, the tumor necrosis factor/nerve growth factor (TNF/NGF) family can activate or inhibit cell death, as well as regulate proliferation and differentiation. The cell response depends on the type of cell, its stage of

differentiation and transformation status, which surface receptors are stimulated, and the types of stimuli acting on the cell (Smith, A. et al. (1994) Cell 76:959-962; and Nocentini, G. et al. (1997) Proc. Natl. Acad. Sci. USA 94:6216-6221).

Neighboring cells in a tissue compete for growth factors, and when provided with "unlimited" quantities in a perfused system will grow to even higher cell densities before reaching density-dependent inhibition of cell division. Cells often demonstrate an anchorage dependence of cell division as well. This anchorage dependence may be associated with the formation of focal contacts linking the cytoskeleton with the extracellular matrix (ECM). The expression of ECM components can be stimulated by growth factors. For example, TGF-β stimulates fibroblasts to produce a variety of ECM proteins, including fibronectin, collagen, and tenascin (Pearson, C.A. et al. (1988) EMBO J. 7:2677-2981). In fact, for some cell types specific ECM molecules, such as laminin or fibronectin, may act as growth factors. Tenascin-C and -R, expressed in developing and lesioned neural tissue, provide stimulatory/anti-adhesive or inhibitory properties, respectively, for axonal growth (Faissner, A. (1997) Cell Tissue Res. 290:331-341).

Cancers are associated with the activation of oncogenes which are derived from normal cellular genes. These oncogenes encode oncoproteins which convert normal cells into malignant cells. Some oncoproteins are mutant isoforms of the normal protein, and other oncoproteins are abnormally expressed with respect to location or amount of expression. The latter category of oncoprotein causes cancer by altering transcriptional control of cell proliferation. Five classes of oncoproteins are known to affect cell cycle controls. These classes include growth factors, growth factor receptors, intracellular signal transducers, nuclear transcription factors, and cell-cycle control proteins. Viral oncogenes are integrated into the human genome after infection of human cells by certain viruses. Examples of viral oncogenes include v-src, v-abl, and v-fps.

Many oncogenes have been identified and characterized. These include sis, erbA, erbB, her-2, mutated G_s, src, abl, ras, crk, jun, fos, myc, and mutated tumor-suppressor genes such as RB, p53, mdm2, Cip1, p16, and cyclin D. Transformation of normal genes to oncogenes may also occur by chromosomal translocation. The Philadelphia chromosome, characteristic of chronic myeloid leukemia and a subset of acute lymphoblastic leukemias, results from a reciprocal translocation between chromosomes 9 and 22 that moves a truncated portion of the proto-oncogene c-abl to the breakpoint cluster region (bcr) on chromosome 22.

Tumor-suppressor genes are involved in regulating cell proliferation. Mutations which cause reduced or loss of function in tumor-suppressor genes result in uncontrolled cell proliferation. For example, the retinoblastoma gene product (RB), in a non-phosphorylated state, binds several early-response genes and suppresses their transcription, thus blocking cell division. Phosphorylation of RB

causes it to dissociate from the genes, releasing the suppression, and allowing cell division to proceed.

Apoptosis

Apoptosis is the genetically controlled process by which unneeded or defective cells undergo programmed cell death. Selective elimination of cells is as important for morphogenesis and tissue remodeling as is cell proliferation and differentiation. Lack of apoptosis may result in hyperplasia and other disorders associated with increased cell proliferation. Apoptosis is also a critical component of the immune response. Immune cells such as cytotoxic T-cells and natural killer cells prevent the spread of disease by inducing apoptosis in tumor cells and virus-infected cells. In addition, immune cells that fail to distinguish self molecules from foreign molecules must be eliminated by apoptosis to avoid an autoimmune response.

Apoptotic cells undergo distinct morphological changes. Hallmarks of apoptosis include cell shrinkage, nuclear and cytoplasmic condensation, and alterations in plasma membrane topology. Biochemically, apoptotic cells are characterized by increased intracellular calcium concentration, fragmentation of chromosomal DNA, and expression of novel cell surface components.

The molecular mechanisms of apoptosis are highly conserved, and many of the key protein regulators and effectors of apoptosis have been identified. Apoptosis generally proceeds in response to a signal which is transduced intracellularly and results in altered patterns of gene expression and protein activity. Signaling molecules such as hormones and cytokines are known both to stimulate and to inhibit apoptosis through interactions with cell surface receptors. Transcription factors also play an important role in the onset of apoptosis. A number of downstream effector molecules, particularly proteases such as the cysteine proteases called caspases, have been implicated in the degradation of cellular components and the proteolytic activation of other apoptotic effectors.

Aging and Senescence

Studies of the aging process or senescence have shown a number of characteristic cellular and molecular changes (Fauci et al. (1998) Harrison's Principles of Internal Medicine, McGraw-Hill, New York NY, p.37). These characteristics include increases in chromosome structural abnormalities, DNA cross-linking, incidence of single-stranded breaks in DNA, losses in DNA methylation, and degradation of telomere regions. In addition to these DNA changes, post-translational alterations of proteins increase including, deamidation, oxidation, cross-linking, and nonenzymatic glycation. Still further molecular changes occur in the mitochondria of aging cells through deterioration of structure. These changes eventually contribute to decreased function in every organ of the body.

Biochemical Pathway Molecules

SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68

encode, for example, biochemical pathway molecules.

Biochemical pathways are responsible for regulating metabolism, growth and development, protein secretion and trafficking, environmental responses, and ecological interactions including immune response and response to parasites.

DNA replication

Deoxyribonucleic acid (DNA), the genetic material, is found in both the nucleus and mitochondria of human cells. The bulk of human DNA is nuclear, in the form of linear chromosomes, while mitochondrial DNA is circular. DNA replication begins at specific sites called origins of replication. Bidirectional synthesis occurs from the origin via two growing forks that move in opposite directions. Replication is semi-conservative, with each daughter duplex containing one old strand and its newly synthesized complementary partner. Proteins involved in DNA replication include DNA polymerases, DNA primase, telomerase, DNA helicase, topoisomerases, DNA ligases, replication factors, and DNA-binding proteins.

DNA Recombination and Repair

Cells are constantly faced with replication errors and environmental assault (such as ultraviolet irradiation) that can produce DNA damage. Damage to DNA consists of any change that modifies the structure of the molecule. Changes to DNA can be divided into two general classes, single base changes and structural distortions. Any damage to DNA can produce a mutation, and the mutation may produce a disorder, such as cancer.

Changes in DNA are recognized by repair systems within the cell. These repair systems act to correct the damage and thus prevent any deleterious affects of a mutational event. Repair systems can be divided into three general types, direct repair, excision repair, and retrieval systems. Proteins involved in DNA repair include DNA polymerase, excision repair proteins, excision and cross link repair proteins, recombination and repair proteins, RAD51 proteins, and BLN and WRN proteins that are homologs of RecQ helicase. When the repair systems are eliminated, cells become exceedingly sensitive to environmental mutagens, such as ultraviolet irradiation. Patients with disorders associated with a loss in DNA repair systems often exhibit a high sensitivity to environmental mutagens. Examples of such disorders include xeroderma pigmentosum (XP), Bloom's syndrome (BS), and Werner's syndrome (WS) (Yamagata, K. et al. (1998) Proc. Natl. Acad. Sci. USA 95:8733-8738), ataxia telangiectasia, Cockayne's syndrome, and Fanconi's anemia.

Recombination is the process whereby new DNA sequences are generated by the movements of large pieces of DNA. In homologous recombination, which occurs during meiosis and DNA repair, parent DNA duplexes align at regions of sequence similarity, and new DNA molecules form by the breakage and joining of homologous segments. Proteins involved include RAD51 recombinase. In site-

specific recombination, two specific but not necessarily homologous DNA sequences are exchanged. In the immune system this process generates a diverse collection of antibody and T cell receptor genes. Proteins involved in site-specific recombination in the immune system include recombination activating genes 1 and 2 (RAG1 and RAG2). A defect in immune system site-specific recombination causes severe combined immunodeficiency disease in mice.

RNA Metabolism

Ribonucleic acid (RNA) is a linear single-stranded polymer of four nucleotides, ATP, CTP, UTP, and GTP. In most organisms, RNA is transcribed as a copy of DNA, the genetic material of the organism. In retroviruses RNA rather than DNA serves as the genetic material. RNA copies of the genetic material encode proteins or serve various structural, catalytic, or regulatory roles in organisms. RNA is classified according to its cellular localization and function. Messenger RNAs (mRNAs) encode polypeptides. Ribosomal RNAs (rRNAs) are assembled, along with ribosomal proteins, into ribosomes, which are cytoplasmic particles that translate mRNA into polypeptides. Transfer RNAs (tRNAs) are cytosolic adaptor molecules that function in mRNA translation by recognizing both an mRNA codon and the amino acid that matches that codon. Heterogeneous nuclear RNAs (hnRNAs) include mRNA precursors and other nuclear RNAs of various sizes. Small nuclear RNAs (snRNAs) are a part of the nuclear spliceosome complex that removes intervening, non-coding sequences (introns) and rejoins exons in pre-mRNAs.

RNA Transcription

The transcription process synthesizes an RNA copy of DNA. Proteins involved include multi-subunit RNA polymerases, transcription factors IIA, IIB, IID, IIE, IIF, IIH, and IIJ. Many transcription factors incorporate DNA-binding structural motifs which comprise either α-helices or β-sheets that bind to the major groove of DNA. Four well-characterized structural motifs are helix-turn-helix, zinc finger, leucine zipper, and helix-loop-helix.

RNA Processing

Various proteins are necessary for processing of transcribed RNAs in the nucleus. Pre-mRNA processing steps include capping at the 5' end with methylguanosine, polyadenylating the 3' end, and splicing to remove introns. The spliceosomal complex is comprised of five small nuclear ribonucleoprotein particles (snRNPs) designated U1, U2, U4, U5, and U6. Each snRNP contains a single species of snRNA and about ten proteins. The RNA components of some snRNPs recognize and base-pair with intron consensus sequences. The protein components mediate spliceosome assembly and the splicing reaction. Autoantibodies to snRNP proteins are found in the blood of patients with systemic lupus erythematosus (Stryer, L. (1995) Biochemistry W.H. Freeman and Company, New York NY, p. 863).

Heterogeneous nuclear ribonucleoproteins (hnRNPs) have been identified that have roles in splicing, exporting of the mature RNAs to the cytoplasm, and mRNA translation (Biamonti, G. et al. (1998) Clin. Exp. Rheumatol. 16:317-326). Some examples of hnRNPs include the yeast proteins Hrp1p, involved in cleavage and polyadenylation at the 3' end of the RNA; Cbp80p, involved in capping the 5' end of the RNA; and Npl3p, a homolog of mammalian hnRNP A1, involved in export of mRNA from the nucleus (Shen, E.C. et al. (1998) Genes Dev. 12:679-691). HnRNPs have been shown to be important targets of the autoimmune response in rheumatic diseases (Biamonti, supra).

Many snRNP proteins, hnRNP proteins, and alternative splicing factors are characterized by an RNA recognition motif (RRM). (Reviewed in Birney, E. et al. (1993) Nucleic Acids Res. 21:5803-5816.) The RRM is about 80 amino acids in length and forms four β-strands and two α-helices arranged in an α/β sandwich. The RRM contains a core RNP-1 octapeptide motif along with surrounding conserved sequences.

RNA Stability and Degradation

RNA helicases alter and regulate RNA conformation and secondary structure by using energy derived from ATP hydrolysis to destabilize and unwind RNA duplexes. The most well-characterized and ubiquitous family of RNA helicases is the DEAD-box family, so named for the conserved B-type ATP-binding motif which is diagnostic of proteins in this family. Over 40 DEAD-box helicases have been identified in organisms as diverse as bacteria, insects, yeast, amphibians, mammals, and plants. DEAD-box helicases function in diverse processes such as translation initiation, splicing, ribosome assembly, and RNA editing, transport, and stability. Some DEAD-box helicases play tissue- and stage-specific roles in spermatogenesis and embryogenesis. (Reviewed in Linder, P. et al. (1989) Nature 337:121-122.)

Overexpression of the DEAD-box 1 protein (DDX1) may play a role in the progression of neuroblastoma (Nb) and retinoblastoma (Rb) tumors. Other DEAD-box helicases have been implicated either directly or indirectly in ultraviolet light-induced tumors, B cell lymphoma, and myeloid malignancies. (Reviewed in Godbout, R. et al. (1998) J. Biol. Chem. 273:21161-21168.)

Ribonucleases (RNases) catalyze the hydrolysis of phosphodiester bonds in RNA chains, thus cleaving the RNA. For example, RNase P is a ribonucleoprotein enzyme which cleaves the 5' end of pre-tRNAs as part of their maturation process. RNase H digests the RNA strand of an RNA/DNA hybrid. Such hybrids occur in cells invaded by retroviruses, and RNase H is an important enzyme in the retroviral replication cycle. RNase H domains are often found as a domain associated with reverse transcriptases. RNase activity in serum and cell extracts is elevated in a variety of cancers and infectious diseases (Schein, C.H. (1997) Nat. Biotechnol. 15:529-536). Regulation of RNase activity is being investigated as a means to control tumor angiogenesis, allergic reactions, viral infection and

replication, and fungal infections.

Protein Translation

The eukaryotic ribosome is composed of a 60S (large) subunit and a 40S (small) subunit, which together form the 80S ribosome. In addition to the 18S, 28S, 5S, and 5.8S rRNAs, the ribosome also contains more than fifty proteins. The ribosomal proteins have a prefix which denotes the subunit to which they belong, either L (large) or S (small). Three important sites are identified on the ribosome. The aminoacyl-tRNA site (A site) is where charged tRNAs (with the exception of the initiator-tRNA) bind on arrival at the ribosome. The peptidyl-tRNA site (P site) is where new peptide bonds are formed, as well as where the initiator tRNA binds. The exit site (E site) is where deacylated tRNAs bind prior to their release from the ribosome. (Translation is reviewed in Stryer, L. (1995) Biochemistry, W.H. Freeman and Company, New York NY, pp. 875-908; and Lodish, H. et al. (1995) Molecular Cell Biology, Scientific American Books, New York NY, pp. 119-138.)

tRNA Charging

Protein biosynthesis depends on each amino acid forming a linkage with the appropriate tRNA. The aminoacyl-tRNA synthetases are responsible for the activation and correct attachment of an amino acid with its cognate tRNA. The 20 aminoacyl-tRNA synthetase enzymes can be divided into two structural classes, Class I and Class II. Autoantibodies against aminoacyl-tRNAs are generated by patients with dermatomyositis and polymyositis, and correlate strongly with complicating interstitial lung disease (ILD). These antibodies appear to be generated in response to viral infection, and coxsackie virus has been used to induce experimental viral myositis in animals.

Translation Initiation

Initiation of translation can be divided into three stages. The first stage brings an initiator transfer RNA (Met-tRNA$_f$) together with the 40S ribosomal subunit to form the 43S preinitiation complex. The second stage binds the 43S preinitiation complex to the mRNA, followed by migration of the complex to the correct AUG initiation codon. The third stage brings the 60S ribosomal subunit to the 40S subunit to generate an 80S ribosome at the initiation codon. Regulation of translation primarily involves the first and second stage in the initiation process (Pain, V.M. (1996) Eur. J. Biochem. 236:747-771).

Several initiation factors, many of which contain multiple subunits, are involved in bringing an initiator tRNA and 40S ribosomal subunit together. eIF2, a guanine nucleotide binding protein, recruits the initiator tRNA to the 40S ribosomal subunit. Only when eIF2 is bound to GTP does it associate with the initiator tRNA. eIF2B, a guanine nucleotide exchange protein, is responsible for converting eIF2 from the GDP-bound inactive form to the GTP-bound active form. Two other factors, eIF1A and eIF3 bind and stabilize the 40S subunit by interacting with 18S ribosomal RNA and specific ribosomal

structural proteins. eIF3 is also involved in association of the 40S ribosomal subunit with mRNA. The Met-tRNA$_f$, eIF1A, eIF3, and 40S ribosomal subunit together make up the 43S preinitiation complex (Pain, supra).

Additional factors are required for binding of the 43S preinitiation complex to an mRNA molecule, and the process is regulated at several levels. eIF4F is a complex consisting of three proteins: eIF4E, eIF4A, and eIF4G. eIF4E recognizes and binds to the mRNA 5'-terminal m^{7}GTP cap, eIF4A is a bidirectional RNA-dependent helicase, and eIF4G is a scaffolding polypeptide. eIF4G has three binding domains. The N-terminal third of eIF4G interacts with eIF4E, the central third interacts with eIF4A, and the C-terminal third interacts with eIF3 bound to the 43S preinitiation complex. Thus, eIF4G acts as a bridge between the 40S ribosomal subunit and the mRNA (Hentze, M.W. (1997) Science 275:500-501).

The ability of eIF4F to initiate binding of the 43S preinitiation complex is regulated by structural features of the mRNA. The mRNA molecule has an untranslated region (UTR) between the 5' cap and the AUG start codon. In some mRNAs this region forms secondary structures that impede binding of the 43S preinitiation complex. The helicase activity of eIF4A is thought to function in removing this secondary structure to facilitate binding of the 43S preinitiation complex (Pain, supra).

Translation Elongation

Elongation is the process whereby additional amino acids are joined to the initiator methionine to form the complete polypeptide chain. The elongation factors EF1α, EF1$\beta\gamma$, and EF2 are involved in elongating the polypeptide chain following initiation. EF1α is a GTP-binding protein. In EF1α's GTP-bound form, it brings an aminoacyl-tRNA to the ribosome's A site. The amino acid attached to the newly arrived aminoacyl-tRNA forms a peptide bond with the initiator methionine. The GTP on EF1α is hydrolyzed to GDP, and EF1α-GDP dissociates from the ribosome. EF1$\beta\gamma$ binds EF1α -GDP and induces the dissociation of GDP from EF1α, allowing EF1α to bind GTP and a new cycle to begin.

As subsequent aminoacyl-tRNAs are brought to the ribosome, EF-G, another GTP-binding protein, catalyzes the translocation of tRNAs from the A site to the P site and finally to the E site of the ribosome. This allows the processivity of translation.

Translation Termination

The release factor eRF carries out termination of translation. eRF recognizes stop codons in the mRNA, leading to the release of the polypeptide chain from the ribosome.

Post-Translational Pathways

Proteins may be modified after translation by the addition of phosphate, sugar, prenyl, fatty acid, and other chemical groups. These modifications are often required for proper protein activity. Enzymes involved in post-translational modification include kinases, phosphatases,

glycosyltransferases, and prenyltransferases. The conformation of proteins may also be modified after translation by the introduction and rearrangement of disulfide bonds (rearrangement catalyzed by protein disulfide isomerase), the isomerization of proline sidechains by prolyl isomerase, and by interactions with molecular chaperone proteins.

Proteins may also be cleaved by proteases. Such cleavage may result in activation, inactivation, or complete degradation of the protein. Proteases include serine proteases, cysteine proteases, aspartic proteases, and metalloproteases. Signal peptidase in the endoplasmic reticulum (ER) lumen cleaves the signal peptide from membrane or secretory proteins that are imported into the ER. Ubiquitin proteases are associated with the ubiquitin conjugation system (UCS), a major pathway for the degradation of cellular proteins in eukaryotic cells and some bacteria. The UCS mediates the elimination of abnormal proteins and regulates the half-lives of important regulatory proteins that control cellular processes such as gene transcription and cell cycle progression. In the UCS pathway, proteins targeted for degradation are conjugated to a ubiquitin, a small heat stable protein. Proteins involved in the UCS include ubiquitin-activating enzyme, ubiquitin-conjugating enzymes, ubiquitin-ligases, and ubiquitin C-terminal hydrolases. The ubiquitinated protein is then recognized and degraded by the proteasome, a large, multisubunit proteolytic enzyme complex, and ubiquitin is released for reutilization by ubiquitin protease.

Lipid Metabolism

Lipids are water-insoluble, oily or greasy substances that are soluble in nonpolar solvents such as chloroform or ether. Neutral fats (triacylglycerols) serve as major fuels and energy stores. Polar lipids, such as phospholipids, sphingolipids, glycolipids, and cholesterol, are key structural components of cell membranes.

Lipid metabolism is involved in human diseases and disorders. In the arterial disease atherosclerosis, fatty lesions form on the inside of the arterial wall. These lesions promote the loss of arterial flexibility and the formation of blood clots (Guyton, A.C. Textbook of Medical Physiology (1991) W.B. Saunders Company, Philadelphia PA, pp.760-763). In Tay-Sachs disease, the GM_2 ganglioside (a sphingolipid) accumulates in lysosomes of the central nervous system due to a lack of the enzyme N-acetylhexosaminidase. Patients suffer nervous system degeneration leading to early death (Fauci, A.S. et al. (1998) Harrison's Principles of Internal Medicine McGraw-Hill, New York NY, p. 2171). The Niemann-Pick diseases are caused by defects in lipid metabolism. Niemann-Pick diseases types A and B are caused by accumulation of sphingomyelin (a sphingolipid) and other lipids in the central nervous system due to a defect in the enzyme sphingomyelinase, leading to neurodegeneration and lung disease. Niemann-Pick disease type C results from a defect in cholesterol transport, leading to the accumulation of sphingomyelin and cholesterol in lysosomes and a secondary reduction in

sphingomyelinase activity. Neurological symptoms such as grand mal seizures, ataxia, and loss of previously learned speech, manifest 1-2 years after birth. A mutation in the NPC protein, which contains a putative cholesterol-sensing domain, was found in a mouse model of Niemann-Pick disease type C (Fauci, supra, p. 2175; Loftus, S.K. et al. (1997) Science 277:232-235). (Lipid metabolism is reviewed in Stryer, L. (1995) Biochemistry, W.H. Freeman and Company, New York NY; Lehninger, A. (1982) Principles of Biochemistry Worth Publishers, Inc., New York NY; and ExPASy "Biochemical Pathways" index of Boehringer Mannheim World Wide Web site.)

Fatty Acid Synthesis

Fatty acids are long-chain organic acids with a single carboxyl group and a long non-polar hydrocarbon tail. Long-chain fatty acids are essential components of glycolipids, phospholipids, and cholesterol, which are building blocks for biological membranes, and of triglycerides, which are biological fuel molecules. Long-chain fatty acids are also substrates for eicosanoid production, and are important in the functional modification of certain complex carbohydrates and proteins. 16-carbon and 18-carbon fatty acids are the most common.

Fatty acid synthesis occurs in the cytoplasm. In the first step, acetyl-Coenzyme A (CoA) carboxylase (ACC) synthesizes malonyl-CoA from acetyl-CoA and bicarbonate. The enzymes which catalyze the remaining reactions are covalently linked into a single polypeptide chain, referred to as the multifunctional enzyme fatty acid synthase (FAS). FAS catalyzes the synthesis of palmitate from acetyl-CoA and malonyl-CoA. FAS contains acetyl transferase, malonyl transferase, β-ketoacetyl synthase, acyl carrier protein, β-ketoacyl reductase, dehydratase, enoyl reductase, and thioesterase activities. The final product of the FAS reaction is the 16-carbon fatty acid palmitate. Further elongation, as well as unsaturation, of palmitate by accessory enzymes of the ER produces the variety of long chain fatty acids required by the individual cell. These enzymes include a NADH-cytochrome b_5 reductase, cytochrome b_5, and a desaturase.

Phospholipid and Triacylglycerol Synthesis

Triacylglycerols, also known as triglycerides and neutral fats, are major energy stores in animals. Triacylglycerols are esters of glycerol with three fatty acid chains. Glycerol-3-phosphate is produced from dihydroxyacetone phosphate by the enzyme glycerol phosphate dehydrogenase or from glycerol by glycerol kinase. Fatty acid-CoA's are produced from fatty acids by fatty acyl-CoA synthetases. Glyercol-3-phosphate is acylated with two fatty acyl-CoA's by the enzyme glycerol phosphate acyltransferase to give phosphatidate. Phosphatidate phosphatase converts phosphatidate to diacylglycerol, which is subsequently acylated to a triacylglyercol by the enzyme diglyceride acyltransferase. Phosphatidate phosphatase and diglyceride acyltransferase form a triacylglyerol synthetase complex bound to the ER membrane.

A major class of phospholipids are the phosphoglycerides, which are composed of a glycerol backbone, two fatty acid chains, and a phosphorylated alcohol. Phosphoglycerides are components of cell membranes. Principal phosphoglycerides are phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, and diphosphatidyl glycerol. Many enzymes involved in phosphoglyceride synthesis are associated with membranes (Meyers, R.A. (1995) Molecular Biology and Biotechnology, VCH Publishers Inc., New York NY, pp. 494-501). Phosphatidate is converted to CDP-diacylglycerol by the enzyme phosphatidate cytidylyltransferase (ExPASy ENZYME EC 2.7.7.41). Transfer of the diacylglycerol group from CDP-diacylglycerol to serine to yield phosphatidyl serine, or to inositol to yield phosphatidyl inositol, is catalyzed by the enzymes CDP-diacylglycerol-serine O-phosphatidyltransferase and CDP-diacylglycerol-inositol 3-phosphatidyltransferase, respectively (ExPASy ENZYME EC 2.7.8.8; ExPASy ENZYME EC 2.7.8.11). The enzyme phosphatidyl serine decarboxylase catalyzes the conversion of phosphatidyl serine to phosphatidyl ethanolamine, using a pyruvate cofactor (Voelker, D.R. (1997) Biochim. Biophys. Acta 1348:236-244). Phosphatidyl choline is formed using diet-derived choline by the reaction of CDP-choline with 1,2-diacylglycerol, catalyzed by diacylglycerol cholinephosphotransferase (ExPASy ENZYME 2.7.8.2).

Sterol, Steroid, and Isoprenoid Metabolism

Cholesterol, composed of four fused hydrocarbon rings with an alcohol at one end, moderates the fluidity of membranes in which it is incorporated. In addition, cholesterol is used in the synthesis of steroid hormones such as cortisol, progesterone, estrogen, and testosterone. Bile salts derived from cholesterol facilitate the digestion of lipids. Cholesterol in the skin forms a barrier that prevents excess water evaporation from the body. Farnesyl and geranylgeranyl groups, which are derived from cholesterol biosynthesis intermediates, are post-translationally added to signal transduction proteins such as ras and protein-targeting proteins such as rab. These modifications are important for the activities of these proteins (Guyton, supra; Stryer, supra, pp. 279-280, 691-702, 934).

Mammals obtain cholesterol derived from both de novo biosynthesis and the diet. The liver is the major site of cholesterol biosynthesis in mammals. Two acetyl-CoA molecules initially condense to form acetoacetyl-CoA, catalyzed by a thiolase. Acetoacetyl-CoA condenses with a third acetyl-CoA to form hydroxymethylglutaryl-CoA (HMG-CoA), catalyzed by HMG-CoA synthase. Conversion of HMG-CoA to cholesterol is accomplished via a series of enzymatic steps known as the mevalonate pathway. The rate-limiting step is the conversion of HMG-CoA to mevalonate by HMG-CoA reductase. The drug lovastatin, a potent inhibitor of HMG-CoA reductase, is given to patients to reduce their serum cholesterol levels. Other mevalonate pathway enzymes include mevalonate kinase, phosphomevalonate kinase, diphosphomevalonate decarboxylase, isopentenyldiphosphate isomerase, dimethylallyl transferase, geranyl transferase, farnesyl-diphosphate farnesyltransferase, squalene

monooxygenase, lanosterol synthase, lathosterol oxidase, and 7-dehydrocholesterol reductase.

Cholesterol is used in the synthesis of steroid hormones such as cortisol, progesterone, aldosterone, estrogen, and testosterone. First, cholesterol is converted to pregnenolone by cholesterol monooxygenases. The other steroid hormones are synthesized from pregnenolone by a series of enzyme-catalyzed reactions including oxidations, isomerizations, hydroxylations, reductions, and demethylations. Examples of these enzymes include steroid Δ-isomerase, 3β-hydroxy-Δ^5-steroid dehydrogenase, steroid 21-monooxygenase, steroid 19-hydroxylase, and 3β-hydroxysteroid dehydrogenase. Cholesterol is also the precursor to vitamin D.

Numerous compounds contain 5-carbon isoprene units derived from the mevalonate pathway intermediate isopentenyl pyrophosphate. Isoprenoid groups are found in vitamin K, ubiquinone, retinal, dolichol phosphate (a carrier of oligosaccharides needed for N-linked glycosylation), and farnesyl and geranylgeranyl groups that modify proteins. Enzymes involved include farnesyl transferase, polyprenyl transferases, dolichyl phosphatase, and dolichyl kinase.

Sphingolipid Metabolism

Sphingolipids are an important class of membrane lipids that contain sphingosine, a long chain amino alcohol. They are composed of one long-chain fatty acid, one polar head alcohol, and sphingosine or sphingosine derivative. The three classes of sphingolipids are sphingomyelins, cerebrosides, and gangliosides. Sphingomyelins, which contain phosphocholine or phosphoethanolamine as their head group, are abundant in the myelin sheath surrounding nerve cells. Galactocerebrosides, which contain a glucose or galactose head group, are characteristic of the brain. Other cerebrosides are found in nonneural tissues. Gangliosides, whose head groups contain multiple sugar units, are abundant in the brain, but are also found in nonneural tissues.

Sphingolipids are built on a sphingosine backbone. Sphingosine is acylated to ceramide by the enzyme sphingosine acetyltransferase. Ceramide and phosphatidyl choline are converted to sphingomyelin by the enzyme ceramide choline phosphotransferase. Cerebrosides are synthesized by the linkage of glucose or galactose to ceramide by a transferase. Sequential addition of sugar residues to ceramide by transferase enzymes yields gangliosides.

Eicosanoid Metabolism

Eicosanoids, including prostaglandins, prostacyclin, thromboxanes, and leukotrienes, are 20-carbon molecules derived from fatty acids. Eicosanoids are signaling molecules which have roles in pain, fever, and inflammation. The precursor of all eicosanoids is arachidonate, which is generated from phospholipids by phospholipase A_2 and from diacylglycerols by diacylglycerol lipase. Leukotrienes are produced from arachidonate by the action of lipoxygenases. Prostaglandin synthase, reductases, and isomerases are responsible for the synthesis of the prostaglandins. Prostaglandins have

roles in inflammation, blood flow, ion transport, synaptic transmission, and sleep. Prostacyclin and the thromboxanes are derived from a precursor prostaglandin by the action of prostacyclin synthase and thromboxane synthases, respectively.

Ketone Body Metabolism

Pairs of acetyl-CoA molecules derived from fatty acid oxidation in the liver can condense to form acetoacetyl-CoA, which subsequently forms acetoacetate, D-3-hydroxybutyrate, and acetone. These three products are known as ketone bodies. Enzymes involved in ketone body metabolism include HMG-CoA synthetase, HMG-CoA cleavage enzyme, D-3-hydroxybutyrate dehydrogenase, acetoacetate decarboxylase, and 3-ketoacyl-CoA transferase. Ketone bodies are a normal fuel supply of the heart and renal cortex. Acetoacetate produced by the liver is transported to cells where the acetoacetate is converted back to acetyl-CoA and enters the citric acid cycle. In times of starvation, ketone bodies produced from stored triacylglyerols become an important fuel source, especially for the brain. Abnormally high levels of ketone bodies are observed in diabetics. Diabetic coma can result if ketone body levels become too great.

Lipid Mobilization

Within cells, fatty acids are transported by cytoplasmic fatty acid binding proteins (Online Mendelian Inheritance in Man (OMIM) *134650 Fatty Acid-Binding Protein 1, Liver; FABP1). Diazepam binding inhibitor (DBI), also known as endozepine and acyl CoA-binding protein, is an endogenous γ-aminobutyric acid (GABA) receptor ligand which is thought to down-regulate the effects of GABA. DBI binds medium- and long-chain acyl-CoA esters with very high affinity and may function as an intracellular carrier of acyl-CoA esters (OMIM *125950 Diazepam Binding Inhibitor; DBI; PROSITE PDOC00686 Acyl-CoA-binding protein signature).

Fat stored in liver and adipose triglycerides may be released by hydrolysis and transported in the blood. Free fatty acids are transported in the blood by albumin. Triacylglycerols and cholesterol esters in the blood are transported in lipoprotein particles. The particles consist of a core of hydrophobic lipids surrounded by a shell of polar lipids and apolipoproteins. The protein components serve in the solubilization of hydrophobic lipids and also contain cell-targeting signals. Lipoproteins include chylomicrons, chylomicron remnants, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). There is a strong inverse correlation between the levels of plasma HDL and risk of premature coronary heart disease.

Triacylglycerols in chylomicrons and VLDL are hydrolyzed by lipoprotein lipases that line blood vessels in muscle and other tissues that use fatty acids. Cell surface LDL receptors bind LDL particles which are then internalized by endocytosis. Absence of the LDL receptor, the cause of the

disease familial hypercholesterolemia, leads to increased plasma cholesterol levels and ultimately to atherosclerosis. Plasma cholesteryl ester transfer protein mediates the transfer of cholesteryl esters from HDL to apolipoprotein B-containing lipoproteins. Cholesteryl ester transfer protein is important in the reverse cholesterol transport system and may play a role in atherosclerosis (Yamashita, S. et al. (1997) Curr. Opin. Lipidol. 8:101-110). Macrophage scavenger receptors, which bind and internalize modified lipoproteins, play a role in lipid transport and may contribute to atherosclerosis (Greaves, D.R. et al. (1998) Curr. Opin. Lipidol. 9:425-432).

Proteins involved in cholesterol uptake and biosynthesis are tightly regulated in response to cellular cholesterol levels. The sterol regulatory element binding protein (SREBP) is a sterol-responsive transcription factor. Under normal cholesterol conditions, SREBP resides in the ER membrane. When cholesterol levels are low, a regulated cleavage of SREBP occurs which releases the extracellular domain of the protein. This cleaved domain is then transported to the nucleus where it activates the transcription of the LDL receptor gene, and genes encoding enzymes of cholesterol synthesis, by binding the sterol regulatory element (SRE) upstream of the genes (Yang, J. et al. (1995) J. Biol. Chem. 270:12152-12161). Regulation of cholesterol uptake and biosynthesis also occurs via the oxysterol-binding protein (OSBP). OSBP is a high-affinity intracellular receptor for a variety of oxysterols that down-regulate cholesterol synthesis and stimulate cholesterol esterification (Lagace, T.A. et al. (1997) Biochem. J. 326:205-213).

Beta-oxidation

Mitochondrial and peroxisomal beta-oxidation enzymes degrade saturated and unsaturated fatty acids by sequential removal of two-carbon units from CoA-activated fatty acids. The main beta-oxidation pathway degrades both saturated and unsaturated fatty acids while the auxiliary pathway performs additional steps required for the degradation of unsaturated fatty acids.

The pathways of mitochondrial and peroxisomal beta-oxidation use similar enzymes, but have different substrate specificities and functions. Mitochondria oxidize short-, medium-, and long-chain fatty acids to produce energy for cells. Mitochondrial beta-oxidation is a major energy source for cardiac and skeletal muscle. In liver, it provides ketone bodies to the peripheral circulation when glucose levels are low as in starvation, endurance exercise, and diabetes (Eaton, S. et al. (1996) Biochem. J. 320:345-357). Peroxisomes oxidize medium-, long-, and very-long-chain fatty acids, dicarboxylic fatty acids, branched fatty acids, prostaglandins, xenobiotics, and bile acid intermediates. The chief roles of peroxisomal beta-oxidation are to shorten toxic lipophilic carboxylic acids to facilitate their excretion and to shorten very-long-chain fatty acids prior to mitochondrial beta-oxidation (Mannaerts, G.P. and P.P. van Veldhoven (1993) Biochimie 75:147-158).

Enzymes involved in beta-oxidation include acyl CoA synthetase, carnitine acyltransferase,

acyl CoA dehydrogenases, enoyl CoA hydratases, L-3-hydroxyacyl CoA dehydrogenase, β-ketothiolase, 2,4-dienoyl CoA reductase, and isomerase.

Lipid Cleavage and Degradation

Triglycerides are hydrolyzed to fatty acids and glycerol by lipases. Lysophospholipases (LPLs) are widely distributed enzymes that metabolize intracellular lipids, and occur in numerous isoforms. Small isoforms, approximately 15-30 kD, function as hydrolases; large isoforms, those exceeding 60 kD, function both as hydrolases and transacylases. A particular substrate for LPLs, lysophosphatidylcholine, causes lysis of cell membranes when it is formed or imported into a cell. LPLs are regulated by lipid factors including acylcarnitine, arachidonic acid, and phosphatidic acid. These lipid factors are signaling molecules important in numerous pathways, including the inflammatory response. (Anderson, R. et al. (1994) Toxicol. Appl. Pharmacol. 125:176-183; Selle, H. et al. (1993); Eur. J. Biochem. 212:411-416.)

The secretory phospholipase A_2 (PLA2) superfamily comprises a number of heterogeneous enzymes whose common feature is to hydrolyze the sn-2 fatty acid acyl ester bond of phosphoglycerides. Hydrolysis of the glycerophospholipids releases free fatty acids and lysophospholipids. PLA2 activity generates precursors for the biosynthesis of biologically active lipids, hydroxy fatty acids, and platelet-activating factor. PLA2 hydrolysis of the sn-2 ester bond in phospholipids generates free fatty acids, such as arachidonic acid and lysophospholipids.

Carbon and Carbohydrate Metabolism

Carbohydrates, including sugars or saccharides, starch, and cellulose, are aldehyde or ketone compounds with multiple hydroxyl groups. The importance of carbohydrate metabolism is demonstrated by the sensitive regulatory system in place for maintenance of blood glucose levels. Two pancreatic hormones, insulin and glucagon, promote increased glucose uptake and storage by cells, and increased glucose release from cells, respectively. Carbohydrates have three important roles in mammalian cells. First, carbohydrates are used as energy stores, fuels, and metabolic intermediates. Carbohydrates are broken down to form energy in glycolysis and are stored as glycogen for later use. Second, the sugars deoxyribose and ribose form part of the structural support of DNA and RNA, respectively. Third, carbohydrate modifications are added to secreted and membrane proteins and lipids as they traverse the secretory pathway. Cell surface carbohydrate-containing macromolecules, including glycoproteins, glycolipids, and transmembrane proteoglycans, mediate adhesion with other cells and with components of the extracellular matrix. The extracellular matrix is comprised of diverse glycoproteins, glycosaminoglycans (GAGs), and carbohydrate-binding proteins which are secreted from the cell and assembled into an organized meshwork in close association with the cell surface. The interaction of the cell with the surrounding matrix profoundly influences cell shape, strength, flexibility,

motility, and adhesion. These dynamic properties are intimately associated with signal transduction pathways controlling cell proliferation and differentiation, tissue construction, and embryonic development.

Carbohydrate metabolism is altered in several disorders including diabetes mellitus, hyperglycemia, hypoglycemia, galactosemia, galactokinase deficiency, and UDP-galactose-4-epimerase deficiency (Fauci, A.S. et al. (1998) Harrison's Principles of Internal Medicine, McGraw-Hill, New York NY, pp. 2208-2209). Altered carbohydrate metabolism is associated with cancer. Reduced GAG and proteoglycan expression is associated with human lung carcinomas (Nackaerts, K. et al. (1997) Int. J. Cancer 74:335-345). The carbohydrate determinants sialyl Lewis A and sialyl Lewis X are frequently expressed on human cancer cells (Kannagi, R. (1997) Glycoconj. J. 14:577-584). Alterations of the N-linked carbohydrate core structure of cell surface glycoproteins are linked to colon and pancreatic cancers (Schwarz, R.E. et al. (1996) Cancer Lett. 107:285-291). Reduced expression of the Sda blood group carbohydrate structure in cell surface glycolipids and glycoproteins is observed in gastrointestinal cancer (Dohi, T. et al. (1996) Int. J. Cancer 67:626-663). (Carbon and carbohydrate metabolism is reviewed in Stryer, L. (1995) Biochemistry W.H. Freeman and Company, New York NY; Lehninger, A.L. (1982) Principles of Biochemistry Worth Publishers Inc., New York NY; and Lodish, H. et al. (1995) Molecular Cell Biology Scientific American Books, New York NY.)

Glycolysis

Enzymes of the glycolytic pathway convert the sugar glucose to pyruvate while simultaneously producing ATP. The pathway also provides building blocks for the synthesis of cellular components such as long-chain fatty acids. After glycolysis, pyrvuate is converted to acetyl-Coenzyme A, which, in aerobic organisms, enters the citric acid cycle. Glycolytic enzymes include hexokinase, phosphoglucose isomerase, phosphofructokinase, aldolase, triose phosphate isomerase, glyceraldehyde 3-phosphate dehydrogenase, phosphoglycerate kinase, phosphoglyceromutase, enolase, and pyruvate kinase. Of these, phosphofructokinase, hexokinase, and pyruvate kinase are important in regulating the rate of glycolysis.

Gluconeogenesis

Gluconeogenesis is the synthesis of glucose from noncarbohydrate precursors such as lactate and amino acids. The pathway, which functions mainly in times of starvation and intense exercise, occurs mostly in the liver and kidney. Responsible enzymes include pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose 1,6-bisphosphatase, and glucose-6-phosphatase.

Pentose Phosphate Pathway

Pentose phosphate pathway enzymes are responsible for generating the reducing agent NADPH, while at the same time oxidizing glucose-6-phosphate to ribose-5-phosphate. Ribose-5-

phosphate and its derivatives become part of important biological molecules such as ATP, Coenzyme A, NAD^+, FAD, RNA, and DNA. The pentose phosphate pathway has both oxidative and non-oxidative branches. The oxidative branch steps, which are catalyzed by the enzymes glucose-6-phosphate dehydrogenase, lactonase, and 6-phosphogluconate dehydrogenase, convert glucose-6-phosphate and $NADP^+$ to ribulose-6-phosphate and NADPH. The non-oxidative branch steps, which are catalyzed by the enzymes phosphopentose isomerase, phosphopentose epimerase, transketolase, and transaldolase, allow the interconversion of three-, four-, five-, six-, and seven-carbon sugars.

Glucouronate Metabolism

Glucuronate is a monosaccharide which, in the form of D-glucuronic acid, is found in the GAGs chondroitin and dermatan. D-glucuronic acid is also important in the detoxification and excretion of foreign organic compounds such as phenol. Enzymes involved in glucuronate metabolism include UDP-glucose dehydrogenase and glucuronate reductase.

Disaccharide Metabolism

Disaccharides must be hydrolyzed to monosaccharides to be digested. Lactose, a disaccharide found in milk, is hydrolyzed to galactose and glucose by the enzyme lactase. Maltose is derived from plant starch and is hydrolyzed to glucose by the enzyme maltase. Sucrose is derived from plants and is hydrolyzed to glucose and fructose by the enzyme sucrase. Trehalose, a disaccharide found mainly in insects and mushrooms, is hydrolyzed to glucose by the enzyme trehalase (OMIM *275360 Trehalase; Ruf, J. et al. (1990) J. Biol. Chem. 265:15034-15039). Lactase, maltase, sucrase, and trehalase are bound to mucosal cells lining the small intestine, where they participate in the digestion of dietary disaccharides. The enzyme lactose synthetase, composed of the catalytic subunit galactosyltransferase and the modifier subunit α-lactalbumin, converts UDP-galactose and glucose to lactose in the mammary glands.

Glycogen, Starch, and Chitin Metabolism

Glycogen is the storage form of carbohydrates in mammals. Mobilization of glycogen maintains glucose levels between meals and during muscular activity. Glycogen is stored mainly in the liver and in skeletal muscle in the form of cytoplasmic granules. These granules contain enzymes that catalyze the synthesis and degradation of glycogen, as well as enzymes that regulate these processes. Enzymes that catalyze the degradation of glycogen include glycogen phosphorylase, a transferase, α-1,6-glucosidase, and phosphoglucomutase. Enzymes that catalyze the synthesis of glycogen include UDP-glucose pyrophosphorylase, glycogen synthetase, a branching enzyme, and nucleoside diphosphokinase. The enzymes of glycogen synthesis and degradation are tightly regulated by the hormones insulin, glucagon, and epinephrine. Starch, a plant-derived polysaccharide, is hydrolyzed to maltose, maltotriose, and α-dextrin by α-amylase, an enzyme secreted by the salivary glands and

pancreas. Chitin is a polysaccharide found in insects and crustacea. A chitotriosidase is secreted by macrophages and may play a role in the degradation of chitin-containing pathogens (Boot, R.G. et al. (1995) J. Biol. Chem. 270:26252-26256).

Peptidoglycans and Glycosaminoglycans

Glycosaminoglycans (GAGs) are anionic linear unbranched polysaccharides composed of repetitive disaccharide units. These repetitive units contain a derivative of an amino sugar, either glucosamine or galactosamine. GAGs exist free or as part of proteoglycans, large molecules composed of a core protein attached to one or more GAGs. GAGs are found on the cell surface, inside cells, and in the extracellular matrix. Changes in GAG levels are associated with several autoimmune diseases including autoimmune thyroid disease, autoimmune diabetes mellitus, and systemic lupus erythematosus (Hansen, C. et al. (1996) Clin. Exp. Rheum. 14 (Suppl. 15):S59-S67). GAGs include chondroitin sulfate, keratan sulfate, heparin, heparan sulfate, dermatan sulfate, and hyaluronan.

The GAG hyaluronan (HA) is found in the extracellular matrix of many cells, especially in soft connective tissues, and is abundant in synovial fluid (Pitsillides, A.A. et al. (1993) Int. J. Exp. Pathol. 74:27-34). HA seems to play important roles in cell regulation, development, and differentiation (Laurent, T.C. and J.R. Fraser (1992) FASEB J. 6:2397-2404). Hyaluronidase is an enzyme that degrades HA to oligosaccharides. Hyaluronidases may function in cell adhesion, infection, angiogenesis, signal transduction, reproduction, cancer, and inflammation.

Proteoglycans, also known as peptidoglycans, are found in the extracellular matrix of connective tissues such as cartilage and are essential for distributing the load in weight-bearing joints. Cell-surface-attached proteoglycans anchor cells to the extracellular matrix. Both extracellular and cell-surface proteoglycans bind growth factors, facilitating their binding to cell-surface receptors and subsequent triggering of signal transduction pathways.

Amino Acid and Nitrogen Metabolism

NH_4^+ is assimilated into amino acids by the actions of two enzymes, glutamate dehydrogenase and glutamine synthetase. The carbon skeletons of amino acids come from the intermediates of glycolysis, the pentose phosphate pathway, or the citric acid cycle. Of the twenty amino acids used in proteins, humans can synthesize only thirteen (nonessential amino acids). The remaining nine must come from the diet (essential amino acids). Enzymes involved in nonessential amino acid biosynthesis include glutamate kinase dehydrogenase, pyrroline carboxylate reductase, asparagine synthetase, phenylalanine oxygenase, methionine adenosyltransferase, adenosylhomocysteinase, cystathionine β-synthase, cystathionine γ-lyase, phosphoglycerate dehydrogenase, phosphoserine transaminase, phosphoserine phosphatase, serine hydroxylmethyltransferase, and glycine synthase.

Metabolism of amino acids takes place almost entirely in the liver, where the amino group is removed by aminotransferases (transaminases), for example, alanine aminotransferase. The amino group is transferred to α-ketoglutarate to form glutamate. Glutamate dehydrogenase converts glutamate to NH_4^+ and α-ketoglutarate. NH_4^+ is converted to urea by the urea cycle which is catalyzed by the enzymes arginase, ornithine transcarbamoylase, arginosuccinate synthetase, and arginosuccinase. Carbamoyl phosphate synthetase is also involved in urea formation. Enzymes involved in the metabolism of the carbon skeleton of amino acids include serine dehydratase, asparaginase, glutaminase, propionyl CoA carboxylase, methylmalonyl CoA mutase, branched-chain α-keto dehydrogenase complex, isovaleryl CoA dehydrogenase, β-methylcrotonyl CoA carboxylase, phenylalanine hydroxylase, p-hydroxylphenylpyruvate hydroxylase, and homogentisate oxidase.

Polyamines, which include spermidine, putrescine, and spermine, bind tightly to nucleic acids and are abundant in rapidly proliferating cells. Enzymes involved in polyamine synthesis include ornithine decarboxylase.

Diseases involved in amino acid and nitrogen metabolism include hyperammonemia, carbamoyl phosphate synthetase deficiency, urea cycle enzyme deficiencies, methylmalonic aciduria, maple syrup disease, alcaptonuria, and phenylketonuria.

Energy Metabolism

Cells derive energy from metabolism of ingested compounds that may be roughly categorized as carbohydrates, fats, or proteins. Energy is also stored in polymers such as triglycerides (fats) and glycogen (carbohydrates). Metabolism proceeds along separate reaction pathways connected by key intermediates such as acetyl coenzyme A (acetyl-CoA). Metabolic pathways feature anaerobic and aerobic degradation, coupled with the energy-requiring reactions such as phosphorylation of adenosine diphosphate (ADP) to the triphosphate (ATP) or analogous phosphorylations of guanosine (GDP/GTP), uridine (UDP/UTP), or cytidine (CDP/CTP). Subsequent dephosphorylation of the triphosphate drives reactions needed for cell maintenance, growth, and proliferation.

Digestive enzymes convert carbohydrates and sugars to glucose; fructose and galactose are converted in the liver to glucose. Enzymes involved in these conversions include galactose-1-phosphate uridyl transferase and UDP-galactose-4 epimerase. In the cytoplasm, glycolysis converts glucose to pyruvate in a series of reactions coupled to ATP synthesis.

Pyruvate is transported into the mitochondria and converted to acetyl-CoA for oxidation via the citric acid cycle, involving pyruvate dehydrogenase components, dihydrolipoyl transacetylase, and dihydrolipoyl dehydrogenase. Enzymes involved in the citric acid cycle include: citrate synthetase, aconitases, isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase complex including transsuccinylases, succinyl CoA synthetase, succinate dehydrogenase, fumarases, and malate dehydrogenase. Acetyl CoA is oxidized to CO_2 with concomitant formation of NADH, $FADH_2$, and

GTP. In oxidative phosphorylation, the transport of electrons from NADH and $FADH_2$ to oxygen by dehydrogenases is coupled to the synthesis of ATP from ADP and P_i by the F_0F_1 ATPase complex in the mitochondrial inner membrane. Enzyme complexes responsible for electron transport and ATP synthesis include the F_0F_1 ATPase complex, ubiquinone(CoQ)-cytochrome c reductase, ubiquinone reductase, cytochrome b, cytochrome c_1, FeS protein, and cytochrome c oxidase.

Triglycerides are hydrolyzed to fatty acids and glycerol by lipases. Glycerol is then phosphorylated to glycerol-3-phosphate by glycerol kinase and glycerol phosphate dehydrogenase, and degraded by the glycolysis. Fatty acids are transported into the mitochondria as fatty acyl-carnitine esters and undergo oxidative degradation.

In addition to metabolic disorders such as diabetes and obesity, disorders of energy metabolism are associated with cancers (Dorward, A. et al. (1997) J. Bioenerg. Biomembr. 29:385-392), autism (Lombard, J. (1998) Med. Hypotheses 50:497-500), neurodegenerative disorders (Alexi, T. et al. (1998) Neuroreport 9:R57-64), and neuromuscular disorders (DiMauro, S. et al. (1998) Biochim. Biophys. Acta 1366:199-210). The myocardium is heavily dependent on oxidative metabolism, so metabolic dysfunction often leads to heart disease (DiMauro, S. and M. Hirano (1998) Curr. Opin. Cardiol. 13:190-197).

For a review of energy metabolism enzymes and intermediates, see Stryer, L. et al. (1995) Biochemistry, W.H. Freeman and Co., San Francisco CA, pp. 443-652. For a review of energy metabolism regulation, see Lodish, H. et al. (1995) Molecular Cell Biology, Scientific American Books, New York NY, pp. 744-770.

Cofactor Metabolism

Cofactors, including coenzymes and prosthetic groups, are small molecular weight inorganic or organic compounds that are required for the action of an enzyme. Many cofactors contain vitamins as a component. Cofactors include thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, nicotinamide adenine dinucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate, lipoamide, and heme. The vitamins biotin and cobalamin are associated with enzymes as well. Heme, a prosthetic group found in myoglobin and hemoglobin, consists of protoporphyrin group bound to iron. Porphyrin groups contain four substituted pyrroles covalently joined in a ring, often with a bound metal atom. Enzymes involved in porphyrin synthesis include δ-aminolevulinate synthase, δ-aminolevulinate dehydrase, porphobilinogen deaminase, and cosynthase. Deficiencies in heme formation cause porphyrias. Heme is broken down as a part of erythrocyte turnover. Enzymes involved in heme degradation include heme oxygenase and biliverdin reductase.

Iron is a required cofactor for many enzymes. Besides the heme-containing enzymes, iron is found in iron-sulfur clusters in proteins including aconitase, succinate dehydrogenase, and NADH-Q reductase. Iron is transported in the blood by the protein transferrin. Binding of transferrin to the

transferrin receptor on cell surfaces allows uptake by receptor mediated endocytosis. Cytosolic iron is bound to ferritin protein.

A molybdenum-containing cofactor (molybdopterin) is found in enzymes including sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Molybdopterin biosynthesis is performed by two molybdenum cofactor synthesizing enzymes. Deficiencies in these enzymes cause mental retardation and lens dislocation. Other diseases caused by defects in cofactor metabolism include pernicious anemia and methylmalonic aciduria.

Secretion and Trafficking

Eukaryotic cells are bound by a lipid bilayer membrane and subdivided into functionally distinct, membrane bound compartments. The membranes maintain the essential differences between the cytosol, the extracellular environment, and the lumenal space of each intracellular organelle. As lipid membranes are highly impermeable to most polar molecules, transport of essential nutrients, metabolic waste products, cell signaling molecules, macromolecules and proteins across lipid membranes and between organelles must be mediated by a variety of transport-associated molecules.

Protein Trafficking

In eukaryotes, some proteins are synthesized on ER-bound ribosomes, co-translationally imported into the ER, delivered from the ER to the Golgi complex for post-translational processing and sorting, and transported from the Golgi to specific intracellular and extracellular destinations. All cells possess a constitutive transport process which maintains homeostasis between the cell and its environment. In many differentiated cell types, the basic machinery is modified to carry out specific transport functions. For example, in endocrine glands, hormones and other secreted proteins are packaged into secretory granules for regulated exocytosis to the cell exterior. In macrophage, foreign extracellular material is engulfed (phagocytosis) and delivered to lysosomes for degradation. In fat and muscle cells, glucose transporters are stored in vesicles which fuse with the plasma membrane only in response to insulin stimulation.

The Secretory Pathway

Synthesis of most integral membrane proteins, secreted proteins, and proteins destined for the lumen of a particular organelle occurs on ER-bound ribosomes. These proteins are co-translationally imported into the ER. The proteins leave the ER via membrane-bound vesicles which bud off the ER at specific sites and fuse with each other (homotypic fusion) to form the ER-Golgi Intermediate Compartment (ERGIC). The ERGIC matures progressively through the *cis*, *medial*, and *trans* cisternal stacks of the Golgi, modifying the enzyme composition by retrograde transport of specific Golgi enzymes. In this way, proteins moving through the Golgi undergo post-translational modification, such as glycosylation. The final Golgi compartment is the Trans-Golgi Network (TGN), where both

membrane and lumenal proteins are sorted for their final destination. Transport vesicles destined for intracellular compartments, such as the lysosome, bud off the TGN. What remains is a secretory vesicle which contains proteins destined for the plasma membrane, such as receptors, adhesion molecules, and ion channels, and secretory proteins, such as hormones, neurotransmitters, and digestive enzymes. Secretory vesicles eventually fuse with the plasma membrane (Glick, B.S. and V. Malhotra (1998) Cell 95:883-889).

The secretory process can be constitutive or regulated. Most cells have a constitutive pathway for secretion, whereby vesicles derived from maturation of the TGN require no specific signal to fuse with the plasma membrane. In many cells, such as endocrine cells, digestive cells, and neurons, vesicle pools derived from the TGN collect in the cytoplasm and do not fuse with the plasma membrane until they are directed to by a specific signal.

Endocytosis

Endocytosis, wherein cells internalize material from the extracellular environment, is essential for transmission of neuronal, metabolic, and proliferative signals; uptake of many essential nutrients; and defense against invading organisms. Most cells exhibit two forms of endocytosis. The first, phagocytosis, is an actin-driven process exemplified in macrophage and neutrophils. Material to be endocytosed contacts numerous cell surface receptors which stimulate the plasma membrane to extend and surround the particle, enclosing it in a membrane-bound phagosome. In the mammalian immune system, IgG-coated particles bind Fc receptors on the surface of phagocytic leukocytes. Activation of the Fc receptors initiates a signal cascade involving src-family cytosolic kinases and the monomeric GTP-binding (G) protein Rho. The resulting actin reorganization leads to phagocytosis of the particle. This process is an important component of the humoral immune response, allowing the processing and presentation of bacterial-derived peptides to antigen-specific T-lymphocytes.

The second form of endocytosis, pinocytosis, is a more generalized uptake of material from the external milieu. Like phagocytosis, pinocytosis is activated by ligand binding to cell surface receptors. Activation of individual receptors stimulates an internal response that includes coalescence of the receptor-ligand complexes and formation of clathrin-coated pits. Invagination of the plasma membrane at clathrin-coated pits produces an endocytic vesicle within the cell cytoplasm. These vesicles undergo homotypic fusion to form an early endosomal (EE) compartment. The tubulovesicular EE serves as a sorting site for incoming material. ATP-driven proton pumps in the EE membrane lowers the pH of the EE lumen (pH 6.3-6.8). The acidic environment causes many ligands to dissociate from their receptors. The receptors, along with membrane and other integral membrane proteins, are recycled back to the plasma membrane by budding off the tubular extensions of the EE in recycling vesicles (RV). This selective removal of recycled components produces a carrier vesicle containing ligand and other

material from the external environment. The carrier vesicle fuses with TGN-derived vesicles which contain hydrolytic enzymes. The acidic environment of the resulting late endosome (LE) activates the hydrolytic enzymes which degrade the ligands and other material. As digestion takes place, the LE fuses with the lysosome where digestion is completed (Mellman, I. (1996) Annu. Rev. Cell Dev. Biol. 12:575-625).

Recycling vesicles may return directly to the plasma membrane. Receptors internalized and returned directly to the plasma membrane have a turnover rate of 2-3 minutes. Some RVs undergo microtubule-directed relocation to a perinuclear site, from which they then return to the plasma membrane. Receptors following this route have a turnover rate of 5-10 minutes. Still other RVs are retained within the cell until an appropriate signal is received (Mellman, supra; and James, D.E. et al. (1994) Trends Cell Biol. 4:120-126).

Vesicle Formation

Several steps in the transit of material along the secretory and endocytic pathways require the formation of transport vesicles. Specifically, vesicles form at the transitional endoplasmic reticulum (tER), the rim of Golgi cisternae, the face of the Trans-Golgi Network (TGN), the plasma membrane (PM), and tubular extensions of the endosomes. The process begins with the budding of a vesicle out of the donor membrane. The membrane-bound vesicle contains proteins to be transported and is surrounded by a protective coat made up of protein subunits recruited from the cytosol. The initial budding and coating processes are controlled by a cytosolic ras-like GTP-binding protein, ADP-ribosylating factor (Arf), and adapter proteins (AP). Different isoforms of both Arf and AP are involved at different sites of budding. Another small G-protein, dynamin, forms a ring complex around the neck of the forming vesicle and may provide the mechanochemical force to accomplish the final step of the budding process. The coated vesicle complex is then transported through the cytosol. During the transport process, Arf-bound GTP is hydrolyzed to GDP and the coat dissociates from the transport vesicle (West, M.A. et al. (1997) J. Cell Biol. 138:1239-1254). Two different classes of coat protein have also been identified. Clathrin coats form on the TGN and PM surfaces, whereas coatomer or COP coats form on the ER and Golgi. COP coats can further be distinguished as COPI, involved in retrograde traffic through the Golgi and from the Golgi to the ER, and COPII, involved in anterograde traffic from the ER to the Golgi (Mellman, supra). The COP coat consists of two major components, a G-protein (Arf or Sar) and coat protomer (coatomer). Coatomer is an equimolar complex of seven proteins, termed alpha-, beta-, beta'-, gamma-, delta-, epsilon- and zeta-COP. (Harter, C. and F.T. Wieland (1998) Proc. Natl. Acad. Sci. USA 95:11649-11654.)

Membrane Fusion

Transport vesicles undergo homotypic or heterotypic fusion in the secretory and endocytotic

pathways. Molecules required for appropriate targeting and fusion of vesicles with their target membrane include proteins incorporated in the vesicle membrane, the target membrane, and proteins recruited from the cytosol. During budding of the vesicle from the donor compartment, an integral membrane protein, VAMP (vesicle-associated membrane protein) is incorporated into the vesicle. Soon after the vesicle uncoats, a cytosolic prenylated GTP-binding protein, Rab (a member of the Ras superfamily), is inserted into the vesicle membrane. GTP-bound Rab proteins are directed into nascent transport vesicles where they interact with VAMP. Following vesicle transport, GTPase activating proteins (GAPs) in the target membrane convert Rab proteins to the GDP-bound form. A cytosolic protein, guanine-nucleotide dissociation inhibitor (GDI) helps return GDP-bound Rab proteins to their membrane of origin. Several Rab isoforms have been identified and appear to associate with specific compartments within the cell. Rab proteins appear to play a role in mediating the function of a viral gene, Rev, which is essential for replication of HIV-1, the virus responsible for AIDS (Flavell, R.A. et al. (1996) Proc. Natl. Acad. Sci. USA 93:4421-4424).

Docking of the transport vesicle with the target membrane involves the formation of a complex between the vesicle SNAP receptor (v-SNARE), target membrane (t-) SNAREs, and certain other membrane and cytosolic proteins. Many of these other proteins have been identified although their exact functions in the docking complex remain uncertain (Tellam, J.T. et al. (1995) J. Biol. Chem. 270:5857-63; and Hata, Y. and T.C. Sudhof (1995) J. Biol. Chem. 270:13022-28). N-ethylmaleimide sensitive factor (NSF) and soluble NSF-attachment protein (α-SNAP and β-SNAP) are two such proteins that are conserved from yeast to man and function in most intracellular membrane fusion reactions. Sec1 represents a family of yeast proteins that function at many different stages in the secretory pathway including membrane fusion. Recently, mammalian homologs of Sec1, called Munc-18 proteins, have been identified (Katagiri, H. et al. (1995) J. Biol. Chem. 270:4963-4966; Hata et al. supra).

The SNARE complex involves three SNARE molecules, one in the vesicular membrane and two in the target membrane. Synaptotagmin is an integral membrane protein in the synaptic vesicle which associates with the t-SNARE syntaxin in the docking complex. Synaptotagmin binds calcium in a complex with negatively charged phospholipids, which allows the cytosolic SNAP protein to displace synaptotagmin from syntaxin and fusion to occur. Thus, synaptotagmin is a negative regulator of fusion in the neuron (Littleton, J.T. et al. (1993) Cell 74:1125-1134). The most abundant membrane protein of synaptic vesicles appears to be the glycoprotein synaptophysin, a 38 kDa protein with four transmembrane domains.

Specificity between a vesicle and its target is derived from the v-SNARE, t-SNAREs, and associated proteins involved. Different isoforms of SNAREs and Rabs show distinct cellular and

subcellular distributions. VAMP-1/synaptobrevin, membrane-anchored synaptosome-associated protein of 25 kDa (SNAP-25), syntaxin-1, Rab3A, Rab15, and Rab23 are predominantly expressed in the brain and nervous system. Different syntaxin, VAMP, and Rab proteins are associated with distinct subcellular compartments and their vesicular carriers.

Nuclear Transport

Transport of proteins and RNA between the nucleus and the cytoplasm occurs through nuclear pore complexes (NPCs). NPC-mediated transport occurs in both directions through the nuclear envelope. All nuclear proteins are imported from the cytoplasm, their site of synthesis. tRNA and mRNA are exported from the nucleus, their site of synthesis, to the cytoplasm, their site of function. Processing of small nuclear RNAs involves export into the cytoplasm, assembly with proteins and modifications such as hypermethylation to produce small nuclear ribonuclear proteins (snRNPs), and subsequent import of the snRNPs back into the nucleus. The assembly of ribosomes requires the initial import of ribosomal proteins from the cytoplasm, their incorporation with RNA into ribosomal subunits, and export back to the cytoplasm. (Görlich, D. and I.W. Mattaj (1996) Science 271:1513-1518.)

The transport of proteins and mRNAs across the NPC is selective, dependent on nuclear localization signals, and generally requires association with nuclear transport factors. Nuclear localization signals (NLS) consist of short stretches of amino acids enriched in basic residues. NLS are found on proteins that are targeted to the nucleus, such as the glucocorticoid receptor. The NLS is recognized by the NLS receptor, importin, which then interacts with the monomeric GTP-binding protein Ran. This NLS protein/receptor/Ran complex navigates the nuclear pore with the help of the homodimeric protein nuclear transport factor 2 (NTF2). NTF2 binds the GDP-bound form of Ran and to multiple proteins of the nuclear pore complex containing FXFG repeat motifs, such as p62. (Paschal, B. et al. (1997) J. Biol. Chem. 272:21534-21539; and Wong, D.H. et al. (1997) Mol. Cell Biol. 17:3755-3767). Some proteins are dissociated before nuclear mRNAs are transported across the NPC while others are dissociated shortly after nuclear mRNA transport across the NPC and are reimported into the nucleus.

Disease Correlation

The etiology of numerous human diseases and disorders can be attributed to defects in the transport or secretion of proteins. For example, abnormal hormonal secretion is linked to disorders such as diabetes insipidus (vasopressin), hyper- and hypoglycemia (insulin, glucagon), Grave's disease and goiter (thyroid hormone), and Cushing's and Addison's diseases (adrenocorticotropic hormone, ACTH). Moreover, cancer cells secrete excessive amounts of hormones or other biologically active peptides. Disorders related to excessive secretion of biologically active peptides by tumor cells include

fasting hypoglycemia due to increased insulin secretion from insulinoma-islet cell tumors; hypertension due to increased epinephrine and norepinephrine secreted from pheochromocytomas of the adrenal medulla and sympathetic paraganglia; and carcinoid syndrome, which is characterized by abdominal cramps, diarrhea, and valvular heart disease caused by excessive amounts of vasoactive substances such as serotonin, bradykinin, histamine, prostaglandins, and polypeptide hormones, secreted from intestinal tumors. Biologically active peptides that are ectopically synthesized in and secreted from tumor cells include ACTH and vasopressin (lung and pancreatic cancers); parathyroid hormone (lung and bladder cancers); calcitonin (lung and breast cancers); and thyroid-stimulating hormone (medullary thyroid carcinoma). Such peptides may be useful as diagnostic markers for tumorigenesis (Schwartz, M.Z. (1997) Semin. Pediatr. Surg. 3:141-146; and Said, S.I. and G.R. Faloona (1975) N. Engl. J. Med. 293:155-160).

Defective nuclear transport may play a role in cancer. The BRCA1 protein contains three potential NLSs which interact with importin alpha, and is transported into the nucleus by the importin/NPC pathway. In breast cancer cells the BRCA1 protein is aberrantly localized in the cytoplasm. The mislocation of the BRCA1 protein in breast cancer cells may be due to a defect in the NPC nuclear import pathway (Chen, C.F. et al. (1996) J. Biol. Chem. 271:32863-32868).

It has been suggested that in some breast cancers, the tumor-suppressing activity of p53 is inactivated by the sequestration of the protein in the cytoplasm, away from its site of action in the cell nucleus. Cytoplasmic wild-type p53 was also found in human cervical carcinoma cell lines. (Moll, U.M. et al. (1992) Proc. Natl. Acad. Sci. USA 89:7262-7266; and Liang, X.H. et al. (1993) Oncogene 8:2645-2652.)

Environmental Responses

Organisms respond to the environment by a number of pathways. Heat shock proteins, including hsp 70, hsp60, hsp90, and hsp 40, assist organisms in coping with heat damage to cellular proteins.

Aquaporins (AQP) are channels that transport water and, in some cases, nonionic small solutes such as urea and glycerol. Water movement is important for a number of physiological processes including renal fluid filtration, aqueous humor generation in the eye, cerebrospinal fluid production in the brain, and appropriate hydration of the lung. Aquaporins are members of the major intrinsic protein (MIP) family of membrane transporters (King, L.S. and P. Agre (1996) Annu. Rev. Physiol. 58:619-648; Ishibashi, K. et al. (1997) J. Biol. Chem. 272:20782-20786). The study of aquaporins may have relevance to understanding edema formation and fluid balance in both normal physiology and disease states (King, supra). Mutations in AQP2 cause autosomal recessive nephrogenic diabetes insipidus (OMIM *107777 Aquaporin 2; AQP2). Reduced AQP4 expression in skeletal muscle may be

associated with Duchenne muscular dystrophy (Frigeri, A. et al. (1998) J. Clin. Invest. 102:695-703). Mutations in AQP0 cause autosomal dominant cataracts in the mouse (OMIM *154050 Major Intrinsic Protein of Lens Fiber; MIP).

The metallothioneins (MTs) are a group of small (61 amino acids), cysteine-rich proteins that bind heavy metals such as cadmium, zinc, mercury, lead, and copper and are thought to play a role in metal detoxification or the metabolism and homeostasis of metals. Arsenite-resistance proteins have been identified in hamsters that are resistant to toxic levels of arsenite (Rossman, T.G. et al. (1997) Mutat. Res. 386:307-314).

Humans respond to light and odors by specific protein pathways. Proteins involved in light perception include rhodopsin, transducin, and cGMP phosphodiesterase. Proteins involved in odor perception include multiple olfactory receptors. Other proteins are important in human Circadian rhythms and responses to wounds.

Immunity and Host Defense

All vertebrates have developed sophisticated and complex immune systems that provide protection from viral, bacterial, fungal and parasitic infections. Included in these systems are the processes of humoral immunity, the complement cascade and the inflammatory response (Paul, W.E. (1993) Fundamental Immunology, Raven Press, Ltd., New York NY, pp.1-20).

The cellular components of the humoral immune system include six different types of leukocytes: monocytes, lymphocytes, polymorphonuclear granulocytes (consisting of neutrophils, eosinophils, and basophils) and plasma cells. Additionally, fragments of megakaryocytes, a seventh type of white blood cell in the bone marrow, occur in large numbers in the blood as platelets.

Leukocytes are formed from two stem cell lineages in bone marrow. The myeloid stem cell line produces granulocytes and monocytes and, the lymphoid stem cell produces lymphocytes. Lymphoid cells travel to the thymus, spleen and lymph nodes, where they mature and differentiate into lymphocytes. Leukocytes are responsible for defending the body against invading pathogens. Neutrophils and monocytes attack invading bacteria, viruses, and other pathogens and destroy them by phagocytosis. Monocytes enter tissues and differentiate into macrophages which are extremely phagocytic. Lymphocytes and plasma cells are a part of the immune system which recognizes specific foreign molecules and organisms and inactivates them, as well as signals other cells to attack the invaders.

Granulocytes and monocytes are formed and stored in the bone marrow until needed. Megakaryocytes are produced in bone marrow, where they fragment into platelets and are released into the bloodstream. The main function of platelets is to activate the blood clotting mechanism. Lymphocytes and plasma cells are produced in various lymphogenous organs, including the lymph

nodes, spleen, thymus, and tonsils.

Both neutrophils and macrophages exhibit chemotaxis towards sites of inflammation. Tissue inflammation in response to pathogen invasion results in production of chemo-attractants for leukocytes, such as endotoxins or other bacterial products, prostaglandins, and products of leukocytes or platelets. .

Basophils participate in the release of the chemicals involved in the inflammatory process. The main function of basophils is secretion of these chemicals to such a degree that they have been referred to as "unicellular endocrine glands". A distinct aspect of basophilic secretion is that the contents of granules go directly into the extracellular environment, not into vacuoles as occurs with neutrophils, eosinophils and monocytes. Basophils have receptors for the Fc fragment of immunoglobulin E (IgE) that are not present on other leukocytes. Crosslinking of membrane IgE with anti-IgE or other ligands triggers degranulation.

Eosinophils are bi- or multi-nucleated white blood cells which contain eosinophilic granules. Their plasma membrane is characterized by Ig receptors, particularly IgG and IgE. Generally, eosinophils are stored in the bone marrow until recruited for use at a site of inflammation or invasion. They have specific functions in parasitic infections and allergic reactions, and are thought to detoxify some of the substances released by mast cells and basophils which cause inflammation. Additionally, they phagocytize antigen-antibody complexes and further help prevent spread of the inflammation.

Macrophages are monocytes that have left the blood stream to settle in tissue. Once monocytes have migrated into tissues, they do not re-enter the bloodstream. The mononuclear phagocyte system is comprised of precursor cells in the bone marrow, monocytes in circulation, and macrophages in tissues. The system is capable of very fast and extensive phagocytosis. A macrophage may phagocytize over 100 bacteria, digest them and extrude residues, and then survive for many more months. Macrophages are also capable of ingesting large particles, including red blood cells and malarial parasites. They increase several-fold in size and transform into macrophages that are characteristic of the tissue they have entered, surviving in tissues for several months.

Mononuclear phagocytes are essential in defending the body against invasion by foreign pathogens, particularly intracellular microorganisms such as M. tuberculosis, listeria, leishmania and toxoplasma. Macrophages can also control the growth of tumorous cells, via both phagocytosis and secretion of hydrolytic enzymes. Another important function of macrophages is that of processing antigen and presenting them in a biochemically modified form to lymphocytes.

The immune system responds to invading microorganisms in two major ways: antibody production and cell mediated responses. Antibodies are immunoglobulin proteins produced by B-lymphocytes which bind to specific antigens and cause inactivation or promote destruction of the antigen by other cells. Cell-mediated immune responses involve T-lymphocytes (T cells) that react

with foreign antigen on the surface of infected host cells. Depending on the type of T cell, the infected cell is either killed or signals are secreted which activate macrophages and other cells to destroy the infected cell (Paul, supra).

T-lymphocytes originate in the bone marrow or liver in fetuses. Precursor cells migrate via the blood to the thymus, where they are processed to mature into T-lymphocytes. This processing is crucial because of positive and negative selection of T cells that will react with foreign antigen and not with self molecules. After processing, T cells continuously circulate in the blood and secondary lymphoid tissues, such as lymph nodes, spleen, certain epithelium-associated tissues in the gastrointestinal tract, respiratory tract and skin. When T-lymphocytes are presented with the complementary antigen, they are stimulated to proliferate and release large numbers of activated T cells into the lymph system and the blood system. These activated T cells can survive and circulate for several days. At the same time, T memory cells are created, which remain in the lymphoid tissue for months or years. Upon subsequent exposure to that specific antigen, these memory cells will respond more rapidly and with a stronger response than induced by the original antigen. This creates an "immunological memory" that can provide immunity for years.

There are two major types of T cells: cytotoxic T cells destroy infected host cells, and helper T cells activate other white blood cells via chemical signals. One class of helper cell, T_H1, activates macrophages to destroy ingested microorganisms, while another, T_H2, stimulates the production of antibodies by B cells.

Cytotoxic T cells directly attack the infected target cell. In virus-infected cells, peptides derived from viral proteins are generated by the proteasome. These peptides are transported into the ER by the transporter associated with antigen processing (TAP) (Pamer, E. and P. Cresswell (1998) Annu. Rev. Immunol. 16:323-358). Once inside the ER, the peptides bind MHC I chains, and the peptide/MHC I complex is transported to the cell surface. Receptors on the surface of T cells bind to antigen presented on cell surface MHC molecules. Once activated by binding to antigen, T cells secrete γ-interferon, a signal molecule that induces the expression of genes necessary for presenting viral (or other) antigens to cytotoxic T cells. Cytotoxic T cells kill the infected cell by stimulating programmed cell death.

Helper T cells constitute up to 75% of the total T cell population. They regulate the immune functions by producing a variety of lymphokines that act on other cells in the immune system and on bone marrow. Among these lymphokines are: interleukins-2,3,4,5,6; granulocyte-monocyte colony stimulating factor, and γ-interferon.

Helper T cells are required for most B cells to respond to antigen. When an activated helper cell contacts a B cell, its centrosome and Golgi apparatus become oriented toward the B cell, aiding the directing of signal molecules, such as transmembrane-bound protein called CD40 ligand, onto the

B cell surface to interact with the CD40 transmembrane protein. Secreted signals also help B cells to proliferate and mature and, in some cases, to switch the class of antibody being produced.

B-lymphocytes (B cells) produce antibodies which react with specific antigenic proteins presented by pathogens. Once activated, B cells become filled with extensive rough endoplasmic reticulum and are known as plasma cells. As with T cells, interaction of B cells with antigen stimulates proliferation of only those B cells which produce antibody specific to that antigen. There are five classes of antibodies, known as immunoglobulins, which together comprise about 20% of total plasma protein. Each class mediates a characteristic biological response after antigen binding. Upon activation by specific antigen B cells switch from making membrane-bound antibody to secretion of that antibody.

Antibodies, or immunoglobulins (Ig), are the founding members of the Ig superfamily and the central components of the humoral immune response. Antibodies are either expressed on the surface of B cells or secreted by B cells into the circulation. Antibodies bind and neutralize blood-borne foreign antigens. The prototypical antibody is a tetramer consisting of two identical heavy polypeptide chains (H-chains) and two identical light polypeptide chains (L-chains) interlinked by disulfide bonds. This arrangement confers the characteristic Y-shape to antibody molecules. Antibodies are classified based on their H-chain composition. The five antibody classes, IgA, IgD, IgE, IgG and IgM, are defined by the α, δ, ϵ, γ, and μ H-chain types. There are two types of L-chains, κ and λ, either of which may associate as a pair with any H-chain pair. IgG, the most common class of antibody found in the circulation, is tetrameric, while the other classes of antibodies are generally variants or multimers of this basic structure.

H-chains and L-chains each contain an N-terminal variable region and a C-terminal constant region. Both H-chains and L-chains contain repeated Ig domains. For example, a typical H-chain contains four Ig domains, three of which occur within the constant region and one of which occurs within the variable region and contributes to the formation of the antigen recognition site. Likewise, a typical L-chain contains two Ig domains, one of which occurs within the constant region and one of which occurs within the variable region. In addition, H chains such as μ have been shown to associate with other polypeptides during differentiation of the B cell.

Antibodies can be described in terms of their two main functional domains. Antigen recognition is mediated by the Fab (antigen binding fragment) region of the antibody, while effector functions are mediated by the Fc (crystallizable fragment) region. Binding of antibody to an antigen, such as a bacterium, triggers the destruction of the antigen by phagocytic white blood cells such as macrophages and neutrophils. These cells express surface receptors that specifically bind to the antibody Fc region and allow the phagocytic cells to engulf, ingest, and degrade the antibody-bound antigen. The Fc receptors expressed by phagocytic cells are single-pass transmembrane glycoproteins

of about 300 to 400 amino acids (Sears, D.W. et al. (1990) J. Immunol. 144:371-378). The extracellular portion of the Fc receptor typically contains two or three Ig domains.

Diseases which cause over- or under-abundance of any one type of leukocyte usually result in the entire immune defense system becoming involved. A well-known autoimmune disease is AIDS (Acquired Immunodeficiency Syndrome) where the number of helper T cells is depleted, leaving the patient susceptible to infection by microorganisms and parasites. Another widespread medical condition attributable to the immune system is that of allergic reactions to certain antigens. Allergic reactions include: hay fever, asthma, anaphylaxis, and urticaria (hives). Leukemias are an excess production of white blood cells, to the point where a major portion of the body's metabolic resources are directed solely at proliferation of white blood cells, leaving other tissues to starve. Leukopenia or agranulocytosis occurs when the bone marrow stops producing white blood cells. This leaves the body unprotected against foreign microorganisms, including those which normally inhabit skin, mucous membranes, and gastrointestinal tract. If all white blood cell production stops completely, infection will occur within two days and death may follow only 1 to 4 days later.

Impaired phagocytosis occurs in several diseases, including monocytic leukemia, systemic lupus, and granulomatous disease. In such a situation, macrophages can phagocytize normally, but the enveloped organism is not killed. A defect in the plasma membrane enzyme which converts oxygen to lethally reactive forms results in abscess formation in liver, lungs, spleen, lymph nodes, and beneath the skin. Eosinophilia is an excess of eosinophils commonly observed in patients with allergies (hay fever, asthma), allergic reactions to drugs, rheumatoid arthritis, and cancers (Hodgkin's disease, lung, and liver cancer) (Isselbacher, K.J. et al. (1994) Harrison's Principles of Internal Medicine, McGraw-Hill, Inc., New York NY).

Host defense is further augmented by the complement system. The complement system serves as an effector system and is involved in infectious agent recognition. It can function as an independent immune network or in conjunction with other humoral immune responses. The complement system is comprised of numerous plasma and membrane proteins that act in a cascade of reaction sequences whereby one component activates the next. The result is a rapid and amplified response to infection through either an inflammatory response or increased phagocytosis.

The complement system has more than 30 protein components which can be divided into functional groupings including modified serine proteases, membrane-binding proteins and regulators of complement activation. Activation occurs through two different pathways the classical and the alternative. Both pathways serve to destroy infectious agents through distinct triggering mechanisms that eventually merge with the involvement of the component C3.

The classical pathway requires antibody binding to infectious agent antigens. The antibodies serve to define the target and initiate the complement system cascade, culminating in the destruction

of the infectious agent. In this pathway, since the antibody guides initiation of the process, the complement can be seen as an effector arm of the humoral immune system.

The alternative pathway of the complement system does not require the presence of pre-existing antibodies for targeting infectious agent destruction. Rather, this pathway, through low levels of an activated component, remains constantly primed and provides surveillance in the non-immune host to enable targeting and destruction of infectious agents. In this case foreign material triggers the cascade, thereby facilitating phagocytosis or lysis (Paul, supra, pp.918-919).

Another important component of host defense is the process of inflammation. Inflammatory responses are divided into four categories on the basis of pathology and include allergic inflammation, cytotoxic antibody mediated inflammation, immune complex mediated inflammation and monocyte mediated inflammation. Inflammation manifests as a combination of each of these forms with one predominating.

Allergic acute inflammation is observed in individuals wherein specific antigens stimulate IgE antibody production. Mast cells and basophils are subsequently activated by the attachment of antigen-IgE complexes, resulting in the release of cytoplasmic granule contents such as histamine. The products of activated mast cells can increase vascular permeability and constrict the smooth muscle of breathing passages, resulting in anaphylaxis or asthma. Acute inflammation is also mediated by cytotoxic antibodies and can result in the destruction of tissue through the binding of complement-fixing antibodies to cells. The responsible antibodies are of the IgG or IgM types. Resultant clinical disorders include autoimmune hemolytic anemia and thrombocytopenia as associated with systemic lupus erythematosis.

Immune complex mediated acute inflammation involves the IgG or IgM antibody types which combine with antigen to activate the complement cascade. When such immune complexes bind to neutrophils and macrophages they activate the respiratory burst to form protein- and vessel-damaging agents such as hydrogen peroxide, hydroxyl radical, hypochlorous acid, and chloramines. Clinical manifestations include rheumatoid arthritis and systemic lupus erythematosus.

In chronic inflammation or delayed-type hypersensitivity, macrophages are activated and process antigen for presentation to T cells that subsequently produce lymphokines and monokines. This type of inflammatory response is likely important for defense against intracellular parasites and certain viruses. Clinical associations include, granulomatous disease, tuberculosis, leprosy, and sarcoidosis (Paul, W.E., supra, pp.1017-1018).

Extracellular Information Transmission Molecules

SEQ ID NO:9 encodes, for example, an extracellular information transmission molecule.

Intercellular communication is essential for the growth and survival of multicellular

organisms, and in particular, for the function of the endocrine, nervous, and immune systems. In addition, intercellular communication is critical for developmental processes such as tissue construction and organogenesis, in which cell proliferation, cell differentiation, and morphogenesis must be spatially and temporally regulated in a precise and coordinated manner. Cells communicate with one another through the secretion and uptake of diverse types of signaling molecules such as hormones, growth factors, neuropeptides, and cytokines.

Hormones

Hormones are signaling molecules that coordinately regulate basic physiological processes from embryogenesis throughout adulthood. These processes include metabolism, respiration, reproduction, excretion, fetal tissue differentiation and organogenesis, growth and development, homeostasis, and the stress response. Hormonal secretions and the nervous system are tightly integrated and interdependent. Hormones are secreted by endocrine glands, primarily the hypothalamus and pituitary, the thyroid and parathyroid, the pancreas, the adrenal glands, and the ovaries and testes.

The secretion of hormones into the circulation is tightly controlled. Hormones are often secreted in diurnal, pulsatile, and cyclic patterns. Hormone secretion is regulated by perturbations in blood biochemistry, by other upstream-acting hormones, by neural impulses, and by negative feedback loops. Blood hormone concentrations are constantly monitored and adjusted to maintain optimal, steady-state levels. Once secreted, hormones act only on those target cells that express specific receptors.

Most disorders of the endocrine system are caused by either hyposecretion or hypersecretion of hormones. Hyposecretion often occurs when a hormone's gland of origin is damaged or otherwise impaired. Hypersecretion often results from the proliferation of tumors derived from hormone-secreting cells. Inappropriate hormone levels may also be caused by defects in regulatory feedback loops or in the processing of hormone precursors. Endocrine malfunction may also occur when the target cell fails to respond to the hormone.

Hormones can be classified biochemically as polypeptides, steroids, eicosanoids, or amines. Polypeptides, which include diverse hormones such as insulin and growth hormone, vary in size and function and are often synthesized as inactive precursors that are processed intracellularly into mature, active forms. Amines, which include epinephrine and dopamine, are amino acid derivatives that function in neuroendocrine signaling. Steroids, which include the cholesterol-derived hormones estrogen and testosterone, function in sexual development and reproduction. Eicosanoids, which include prostaglandins and prostacyclins, are fatty acid derivatives that function in a variety of processes. Most polypeptides and some amines are soluble in the circulation where they are highly susceptible to proteolytic degradation within seconds after their secretion. Steroids and lipids are

insoluble and must be transported in the circulation by carrier proteins. The following discussion will focus primarily on polypeptide hormones.

Hormones secreted by the hypothalamus and pituitary gland play a critical role in endocrine function by coordinately regulating hormonal secretions from other endocrine glands in response to neural signals. Hypothalamic hormones include thyrotropin-releasing hormone, gonadotropin-releasing hormone, somatostatin, growth-hormone releasing factor, corticotropin-releasing hormone, substance P, dopamine, and prolactin-releasing hormone. These hormones directly regulate the secretion of hormones from the anterior lobe of the pituitary. Hormones secreted by the anterior pituitary include adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone, somatotropic hormones such as growth hormone and prolactin, glycoprotein hormones such as thyroid-stimulating hormone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), β-lipotropin, and β-endorphins. These hormones regulate hormonal secretions from the thyroid, pancreas, and adrenal glands, and act directly on the reproductive organs to stimulate ovulation and spermatogenesis. The posterior pituitary synthesizes and secretes antidiuretic hormone (ADH, vasopressin) and oxytocin.

Disorders of the hypothalamus and pituitary often result from lesions such as primary brain tumors, adenomas, infarction associated with pregnancy, hypophysectomy, aneurysms, vascular malformations, thrombosis, infections, immunological disorders, and complications due to head trauma. Such disorders have profound effects on the function of other endocrine glands. Disorders associated with hypopituitarism include hypogonadism, Sheehan syndrome, diabetes insipidus, Kallman's disease, Hand-Schuller-Christian disease, Letterer-Siwe disease, sarcoidosis, empty sella syndrome, and dwarfism. Disorders associated with hyperpituitarism include acromegaly, giantism, and syndrome of inappropriate ADH secretion (SIADH), often caused by benign adenomas.

Hormones secreted by the thyroid and parathyroid primarily control metabolic rates and the regulation of serum calcium levels, respectively. Thyroid hormones include calcitonin, somatostatin, and thyroid hormone. The parathyroid secretes parathyroid hormone. Disorders associated with hypothyroidism include goiter, myxedema, acute thyroiditis associated with bacterial infection, subacute thyroiditis associated with viral infection, autoimmune thyroiditis (Hashimoto's disease), and cretinism. Disorders associated with hyperthyroidism include thyrotoxicosis and its various forms, Grave's disease, pretibial myxedema, toxic multinodular goiter, thyroid carcinoma, and Plummer's disease. Disorders associated with hyperparathyroidism include Conn disease (chronic hypercalemia) leading to bone resorption and parathyroid hyperplasia.

Hormones secreted by the pancreas regulate blood glucose levels by modulating the rates of carbohydrate, fat, and protein metabolism. Pancreatic hormones include insulin, glucagon, amylin, γ-aminobutyric acid, gastrin, somatostatin, and pancreatic polypeptide. The principal disorder associated

with pancreatic dysfunction is diabetes mellitus caused by insufficient insulin activity. Diabetes mellitus is generally classified as either Type I (insulin-dependent, juvenile diabetes) or Type II (non-insulin-dependent, adult diabetes). The treatment of both forms by insulin replacement therapy is well known. Diabetes mellitus often leads to acute complications such as hypoglycemia (insulin shock), coma, diabetic ketoacidosis, lactic acidosis, and chronic complications leading to disorders of the eye, kidney, skin, bone, joint, cardiovascular system, nervous system, and to decreased resistance to infection.

The anatomy, physiology, and diseases related to hormonal function are reviewed in McCance, K.L. and S.E. Huether (1994) Pathophysiology: The Biological Basis for Disease in Adults and Children, Mosby-Year Book, Inc., St. Louis MO; Greenspan, F.S. and J.D. Baxter (1994) Basic and Clinical Endocrinology, Appleton and Lange, East Norwalk CT.

Growth Factors

Growth factors are secreted proteins that mediate intercellular communication. Unlike hormones, which travel great distances via the circulatory system, most growth factors are primarily local mediators that act on neighboring cells. Most growth factors contain a hydrophobic N-terminal signal peptide sequence which directs the growth factor into the secretory pathway. Most growth factors also undergo post-translational modifications within the secretory pathway. These modifications can include proteolysis, glycosylation, phosphorylation, and intramolecular disulfide bond formation. Once secreted, growth factors bind to specific receptors on the surfaces of neighboring target cells, and the bound receptors trigger intracellular signal transduction pathways. These signal transduction pathways elicit specific cellular responses in the target cells. These responses can include the modulation of gene expression and the stimulation or inhibition of cell division, cell differentiation, and cell motility.

Growth factors fall into at least two broad and overlapping classes. The broadest class includes the large polypeptide growth factors, which are wide-ranging in their effects. These factors include epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), insulin-like growth factor (IGF), nerve growth factor (NGF), and platelet-derived growth factor (PDGF), each defining a family of numerous related factors. The large polypeptide growth factors, with the exception of NGF, act as mitogens on diverse cell types to stimulate wound healing, bone synthesis and remodeling, extracellular matrix synthesis, and proliferation of epithelial, epidermal, and connective tissues. Members of the TGF-β, EGF, and FGF families also function as inductive signals in the differentiation of embryonic tissue. NGF functions specifically as a neurotrophic factor, promoting neuronal growth and differentiation.

Another class of growth factors includes the hematopoietic growth factors, which are narrow in

their target specificity. These factors stimulate the proliferation and differentiation of blood cells such as B-lymphocytes, T-lymphocytes, erythrocytes, platelets, eosinophils, basophils, neutrophils, macrophages, and their stem cell precursors. These factors include the colony-stimulating factors (G-CSF, M-CSF, GM-CSF, and CSF1-3), erythropoietin, and the cytokines. The cytokines are specialized hematopoietic factors secreted by cells of the immune system and are discussed in detail below.

Growth factors play critical roles in neoplastic transformation of cells in vitro and in tumor progression in vivo. Overexpression of the large polypeptide growth factors promotes the proliferation and transformation of cells in culture. Inappropriate expression of these growth factors by tumor cells in vivo may contribute to tumor vascularization and metastasis. Inappropriate activity of hematopoietic growth factors can result in anemias, leukemias, and lymphomas. Moreover, growth factors are both structurally and functionally related to oncoproteins, the potentially cancer-causing products of proto-oncogenes. Certain FGF and PDGF family members are themselves homologous to oncoproteins, whereas receptors for some members of the EGF, NGF, and FGF families are encoded by proto-oncogenes. Growth factors also affect the transcriptional regulation of both proto-oncogenes and oncosuppressor genes (Pimentel, E. (1994) Handbook of Growth Factors, CRC Press, Ann Arbor MI; McKay, I. and I. Leigh, eds. (1993) Growth Factors: A Practical Approach, Oxford University Press, New York NY; Habenicht, A., ed. (1990) Growth Factors, Differentiation Factors, and Cytokines, Springer-Verlag, New York NY).

In addition, some of the large polypeptide growth factors play crucial roles in the induction of the primordial germ layers in the developing embryo. This induction ultimately results in the formation of the embryonic mesoderm, ectoderm, and endoderm which in turn provide the framework for the entire adult body plan. Disruption of this inductive process would be catastrophic to embryonic development.

Small Peptide Factors - Neuropeptides and Vasomediators

Neuropeptides and vasomediators (NP/VM) comprise a family of small peptide factors, typically of 20 amino acids or less. These factors generally function in neuronal excitation and inhibition of vasoconstriction/vasodilation, muscle contraction, and hormonal secretions from the brain and other endocrine tissues. Included in this family are neuropeptides and neuropeptide hormones such as bombesin, neuropeptide Y, neurotensin, neuromedin N, melanocortins, opioids, galanin, somatostatin, tachykinins, urotensin II and related peptides involved in smooth muscle stimulation, vasopressin, vasoactive intestinal peptide, and circulatory system-borne signaling molecules such as angiotensin, complement, calcitonin, endothelins, formyl-methionyl peptides, glucagon, cholecystokinin, gastrin, and many of the peptide hormones discussed above. NP/VMs can transduce signals directly, modulate the activity or release of other neurotransmitters and hormones, and

act as catalytic enzymes in signaling cascades. The effects of NP/VMs range from extremely brief to long-lasting. (Reviewed in Martin, C.R. et al. (1985) Endocrine Physiology, Oxford University Press, New York NY, pp. 57-62.)

Cytokines

Cytokines comprise a family of signaling molecules that modulate the immune system and the inflammatory response. Cytokines are usually secreted by leukocytes, or white blood cells, in response to injury or infection. Cytokines function as growth and differentiation factors that act primarily on cells of the immune system such as B- and T-lymphocytes, monocytes, macrophages, and granulocytes. Like other signaling molecules, cytokines bind to specific plasma membrane receptors and trigger intracellular signal transduction pathways which alter gene expression patterns. There is considerable potential for the use of cytokines in the treatment of inflammation and immune system disorders.

Cytokine structure and function have been extensively characterized in vitro. Most cytokines are small polypeptides of about 30 kilodaltons or less. Over 50 cytokines have been identified from human and rodent sources. Examples of cytokine subfamilies include the interferons (IFN-α, -β, and -γ), the interleukins (IL1-IL13), the tumor necrosis factors (TNF-α and -β), and the chemokines. Many cytokines have been produced using recombinant DNA techniques, and the activities of individual cytokines have been determined in vitro. These activities include regulation of leukocyte proliferation, differentiation, and motility.

The activity of an individual cytokine in vitro may not reflect the full scope of that cytokine's activity in vivo. Cytokines are not expressed individually in vivo but are instead expressed in combination with a multitude of other cytokines when the organism is challenged with a stimulus. Together, these cytokines collectively modulate the immune response in a manner appropriate for that particular stimulus. Therefore, the physiological activity of a cytokine is determined by the stimulus itself and by complex interactive networks among co-expressed cytokines which may demonstrate both synergistic and antagonistic relationships.

Chemokines comprise a cytokine subfamily with over 30 members. (Reviewed in Wells, T. N.C. and M.C. Peitsch (1997) J. Leukoc. Biol. 61:545-550.) Chemokines were initially identified as chemotactic proteins that recruit monocytes and macrophages to sites of inflammation. Recent evidence indicates that chemokines may also play key roles in hematopoiesis and HIV-1 infection. Chemokines are small proteins which range from about 6-15 kilodaltons in molecular weight. Chemokines are further classified as C, CC, CXC, or CX_3C based on the number and position of critical cysteine residues. The CC chemokines, for example, each contain a conserved motif consisting of two consecutive cysteines followed by two additional cysteines which occur downstream at 24- and 16-residue intervals, respectively (ExPASy PROSITE database, documents PS00472 and PDOC00434).

The presence and spacing of these four cysteine residues are highly conserved, whereas the intervening residues diverge significantly. However, a conserved tyrosine located about 15 residues downstream of the cysteine doublet seems to be important for chemotactic activity. Most of the human genes encoding CC chemokines are clustered on chromosome 17, although there are a few examples of CC chemokine genes that map elsewhere. Other chemokines include lymphotactin (C chemokine); macrophage chemotactic and activating factor (MCAF/MCP-1; CC chemokine); platelet factor 4 and IL-8 (CXC chemokines); and fractalkine and neurotractin (CX_3C chemokines). (Reviewed in Luster, A.D. (1998) N. Engl. J. Med. 338:436-445.)

Receptor Molecules

SEQ ID NO:10 and SEQ ID NO:11 encode, for example, receptor molecules.

The term receptor describes proteins that specifically recognize other molecules. The category is broad and includes proteins with a variety of functions. The bulk of receptors are cell surface proteins which bind extracellular ligands and produce cellular responses in the areas of growth, differentiation, endocytosis, and immune response. Other receptors facilitate the selective transport of proteins out of the endoplasmic reticulum and localize enzymes to particular locations in the cell. The term may also be applied to proteins which act as receptors for ligands with known or unknown chemical composition and which interact with other cellular components. For example, the steroid hormone receptors bind to and regulate transcription of DNA.

Regulation of cell proliferation, differentiation, and migration is important for the formation and function of tissues. Regulatory proteins such as growth factors coordinately control these cellular processes and act as mediators in cell-cell signaling pathways. Growth factors are secreted proteins that bind to specific cell-surface receptors on target cells. The bound receptors trigger intracellular signal transduction pathways which activate various downstream effectors that regulate gene expression, cell division, cell differentiation, cell motility, and other cellular processes.

Cell surface receptors are typically integral plasma membrane proteins. These receptors recognize hormones such as catecholamines; peptide hormones; growth and differentiation factors; small peptide factors such as thyrotropin-releasing hormone; galanin, somatostatin, and tachykinins; and circulatory system-borne signaling molecules. Cell surface receptors on immune system cells recognize antigens, antibodies, and major histocompatibility complex (MHC)-bound peptides. Other cell surface receptors bind ligands to be internalized by the cell. This receptor-mediated endocytosis functions in the uptake of low density lipoproteins (LDL), transferrin, glucose- or mannose-terminal glycoproteins, galactose-terminal glycoproteins, immunoglobulins, phosphovitellogenins, fibrin, proteinase-inhibitor complexes, plasminogen activators, and thrombospondin (Lodish, H. et al. (1995)

Molecular Cell Biology, Scientific American Books, New York NY, p. 723; Mikhailenko, I. et al. (1997) J. Biol. Chem. 272:6784-6791).

Receptor Protein Kinases

Many growth factor receptors, including receptors for epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, as well as the growth modulator α-thrombin, contain intrinsic protein kinase activities. When growth factor binds to the receptor, it triggers the autophosphorylation of a serine, threonine, or tyrosine residue on the receptor. These phosphorylated sites are recognition sites for the binding of other cytoplasmic signaling proteins. These proteins participate in signaling pathways that eventually link the initial receptor activation at the cell surface to the activation of a specific intracellular target molecule. In the case of tyrosine residue autophosphorylation, these signaling proteins contain a common domain referred to as a Src homology (SH) domain. SH2 domains and SH3 domains are found in phospholipase C-γ, PI-3-K p85 regulatory subunit, Ras-GTPase activating protein, and $pp60^{c\text{-}src}$ (Lowenstein, E.J. et al. (1992) Cell 70:431-442). The cytokine family of receptors share a different common binding domain and include transmembrane receptors for growth hormone (GH), interleukins, erythropoietin, and prolactin.

Other receptors and second messenger-binding proteins have intrinsic serine/threonine protein kinase activity. These include activin/TGF-β/BMP-superfamily receptors, calcium- and diacylglycerol-activated/phospholipid-dependant protein kinase (PK-C), and RNA-dependant protein kinase (PK-R). In addition, other serine/threonine protein kinases, including nematode Twitchin, have fibronectin-like, immunoglobulin C2-like domains.

G-Protein Coupled Receptors

G-protein coupled receptors (GPCRs) are integral membrane proteins characterized by the presence of seven hydrophobic transmembrane domains which span the plasma membrane and form a bundle of antiparallel alpha (α) helices. These proteins range in size from under 400 to over 1000 amino acids (Strosberg, A.D. (1991) Eur. J. Biochem. 196:1-10; Coughlin, S.R. (1994) Curr. Opin. Cell Biol. 6:191-197). The amino-terminus of the GPCR is extracellular, of variable length and often glycosylated; the carboxy-terminus is cytoplasmic and generally phosphorylated. Extracellular loops of the GPCR alternate with intracellular loops and link the transmembrane domains. The most conserved domains of GPCRs are the transmembrane domains and the first two cytoplasmic loops. The transmembrane domains account for structural and functional features of the receptor. In most cases, the bundle of α helices forms a binding pocket. In addition, the extracellular N-terminal segment or one or more of the three extracellular loops may also participate in ligand binding. Ligand binding activates the receptor by inducing a conformational change in intracellular portions of the receptor. The activated receptor, in turn, interacts with an intracellular heterotrimeric guanine nucleotide binding (G)

protein complex which mediates further intracellular signaling activities, generally the production of second messengers such as cyclic AMP (cAMP), phospholipase C, inositol triphosphate, or interactions with ion channel proteins (Baldwin, J.M. (1994) Curr. Opin. Cell Biol. 6:180-190).

GPCRs include those for acetylcholine, adenosine, epinephrine and norepinephrine, bombesin, bradykinin, chemokines, dopamine, endothelin, γ-aminobutyric acid (GABA), follicle-stimulating hormone (FSH), glutamate, gonadotropin-releasing hormone (GnRH), hepatocyte growth factor, histamine, leukotrienes, melanocortins, neuropeptide Y, opioid peptides, opsins, prostanoids, serotonin, somatostatin, tachykinins, thrombin, thyrotropin-releasing hormone (TRH), vasoactive intestinal polypeptide family, vasopressin and oxytocin, and orphan receptors.

GPCR mutations, which may cause loss of function or constitutive activation, have been associated with numerous human diseases (Coughlin, supra). For instance, retinitis pigmentosa may arise from mutations in the rhodopsin gene. Rhodopsin is the retinal photoreceptor which is located within the discs of the eye rod cell. Parma, J. et al. (1993, Nature 365:649-651) report that somatic activating mutations in the thyrotropin receptor cause hyperfunctioning thyroid adenomas and suggest that certain GPCRs susceptible to constitutive activation may behave as protooncogenes.

Nuclear Receptors

Nuclear receptors bind small molecules such as hormones or second messengers, leading to increased receptor-binding affinity to specific chromosomal DNA elements. In addition the affinity for other nuclear proteins may also be altered. Such binding and protein-protein interactions may regulate and modulate gene expression. Examples of such receptors include the steroid hormone receptors family, the retinoic acid receptors family, and the thyroid hormone receptors family.

Ligand-Gated Receptor Ion Channels

Ligand-gated receptor ion channels fall into two categories. The first category, extracellular ligand-gated receptor ion channels (ELGs), rapidly transduce neurotransmitter-binding events into electrical signals, such as fast synaptic neurotransmission. ELG function is regulated by post-translational modification. The second category, intracellular ligand-gated receptor ion channels (ILGs), are activated by many intracellular second messengers and do not require post-translational modification(s) to effect a channel-opening response.

ELGs depolarize excitable cells to the threshold of action potential generation. In non-excitable cells, ELGs permit a limited calcium ion-influx during the presence of agonist. ELGs include channels directly gated by neurotransmitters such as acetylcholine, L-glutamate, glycine, ATP, serotonin, GABA, and histamine. ELG genes encode proteins having strong structural and functional similarities. ILGs are encoded by distinct and unrelated gene families and include receptors for cAMP, cGMP, calcium ions, ATP, and metabolites of arachidonic acid.

Macrophage Scavenger Receptors

Macrophage scavenger receptors with broad ligand specificity may participate in the binding of low density lipoproteins (LDL) and foreign antigens. Scavenger receptors types I and II are trimeric membrane proteins with each subunit containing a small N-terminal intracellular domain, a transmembrane domain, a large extracellular domain, and a C-terminal cysteine-rich domain. The extracellular domain contains a short spacer domain, an α-helical coiled-coil domain, and a triple helical collagenous domain. These receptors have been shown to bind a spectrum of ligands, including chemically modified lipoproteins and albumin, polyribonucleotides, polysaccharides, phospholipids, and asbestos (Matsumoto, A. et al. (1990) Proc. Natl. Acad. Sci. USA 87:9133-9137; Elomaa, O. et al. (1995) Cell 80:603-609). The scavenger receptors are thought to play a key role in atherogenesis by mediating uptake of modified LDL in arterial walls, and in host defense by binding bacterial endotoxins, bacteria, and protozoa.

T-Cell Receptors

T cells play a dual role in the immune system as effectors and regulators, coupling antigen recognition with the transmission of signals that induce cell death in infected cells and stimulate proliferation of other immune cells. Although a population of T cells can recognize a wide range of different antigens, an individual T cell can only recognize a single antigen and only when it is presented to the T cell receptor (TCR) as a peptide complexed with a major histocompatibility molecule (MHC) on the surface of an antigen presenting cell. The TCR on most T cells consists of immunoglobulin-like integral membrane glycoproteins containing two polypeptide subunits, α and β, of similar molecular weight. Both TCR subunits have an extracellular domain containing both variable and constant regions, a transmembrane domain that traverses the membrane once, and a short intracellular domain (Saito, H. et al. (1984) Nature 309:757-762). The genes for the TCR subunits are constructed through somatic rearrangement of different gene segments. Interaction of antigen in the proper MHC context with the TCR initiates signaling cascades that induce the proliferation, maturation, and function of cellular components of the immune system (Weiss, A. (1991) Annu. Rev. Genet. 25:487-510). Rearrangements in TCR genes and alterations in TCR expression have been noted in lymphomas, leukemias, autoimmune disorders, and immunodeficiency disorders (Aisenberg, A.C. et al. (1985) N. Engl. J. Med. 313:529-533; Weiss, supra).

Intracellular Signaling Molecules

SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, and SEQ ID NO:18 encode, for example, intracellular signaling molecules.

Intracellular signaling is the general process by which cells respond to extracellular signals

(hormones, neurotransmitters, growth and differentiation factors, etc.) through a cascade of biochemical reactions that begins with the binding of a signaling molecule to a cell membrane receptor and ends with the activation of an intracellular target molecule. Intermediate steps in the process involve the activation of various cytoplasmic proteins by phosphorylation via protein kinases, and their deactivation by protein phosphatases, and the eventual translocation of some of these activated proteins to the cell nucleus where the transcription of specific genes is triggered. The intracellular signaling process regulates all types of cell functions including cell proliferation, cell differentiation, and gene transcription, and involves a diversity of molecules including protein kinases and phosphatases, and second messenger molecules, such as cyclic nucleotides, calcium-calmodulin, inositol, and various mitogens, that regulate protein phosphorylation.

Protein Phosphorylation

Protein kinases and phosphatases play a key role in the intracellular signaling process by controlling the phosphorylation and activation of various signaling proteins. The high energy phosphate for this reaction is generally transferred from the adenosine triphosphate molecule (ATP) to a particular protein by a protein kinase and removed from that protein by a protein phosphatase. Protein kinases are roughly divided into two groups: those that phosphorylate tyrosine residues (protein tyrosine kinases, PTK) and those that phosphorylate serine or threonine residues (serine/threonine kinases, STK). A few protein kinases have dual specificity for serine/threonine and tyrosine residues. Almost all kinases contain a conserved 250-300 amino acid catalytic domain containing specific residues and sequence motifs characteristic of the kinase family (Hardie, G. and S. Hanks (1995) The Protein Kinase Facts Books, Vol I:7-20, Academic Press, San Diego CA).

STKs include the second messenger dependent protein kinases such as the cyclic-AMP dependent protein kinases (PKA), involved in mediating hormone-induced cellular responses; calcium-calmodulin (CaM) dependent protein kinases, involved in regulation of smooth muscle contraction, glycogen breakdown, and neurotransmission; and the mitogen-activated protein kinases (MAP) which mediate signal transduction from the cell surface to the nucleus via phosphorylation cascades. Altered PKA expression is implicated in a variety of disorders and diseases including cancer, thyroid disorders, diabetes, atherosclerosis, and cardiovascular disease (Isselbacher, K.J. et al. (1994) Harrison's Principles of Internal Medicine, McGraw-Hill, New York NY, pp. 416-431, 1887).

PTKs are divided into transmembrane, receptor PTKs and nontransmembrane, non-receptor PTKs. Transmembrane PTKs are receptors for most growth factors. Non-receptor PTKs lack transmembrane regions and, instead, form complexes with the intracellular regions of cell surface receptors. Receptors that function through non-receptor PTKs include those for cytokines and hormones (growth hormone and prolactin) and antigen-specific receptors on T and B lymphocytes. Many of these PTKs were first identified as the products of mutant oncogenes in cancer cells in which

their activation was no longer subject to normal cellular controls. In fact, about one third of the known oncogenes encode PTKs, and it is well known that cellular transformation (oncogenesis) is often accompanied by increased tyrosine phosphorylation activity (Charbonneau, H. and N.K. Tonks (1992) Annu. Rev. Cell Biol. 8:463-493).

An additional family of protein kinases previously thought to exist only in procaryotes is the histidine protein kinase family (HPK). HPKs bear little homology with mammalian STKs or PTKs but have distinctive sequence motifs of their own (Davie, J.R. et al. (1995) J. Biol. Chem. 270:19861-19867). A histidine residue in the N-terminal half of the molecule (region I) is an autophosphorylation site. Three additional motifs located in the C-terminal half of the molecule include an invariant asparagine residue in region II and two glycine-rich loops characteristic of nucleotide binding domains in regions III and IV. Recently a branched chain alpha-ketoacid dehydrogenase kinase has been found with characteristics of HPK in rat (Davie, supra).

Protein phosphatases regulate the effects of protein kinases by removing phosphate groups from molecules previously activated by kinases. The two principal categories of protein phosphatases are the protein (serine/threonine) phosphatases (PPs) and the protein tyrosine phosphatases (PTPs). PPs dephosphorylate phosphoserine/threonine residues and are important regulators of many cAMP-mediated hormone responses (Cohen, P. (1989) Annu. Rev. Biochem. 58:453-508). PTPs reverse the effects of protein tyrosine kinases and play a significant role in cell cycle and cell signaling processes (Charbonneau, supra). As previously noted, many PTKs are encoded by oncogenes, and oncogenesis is often accompanied by increased tyrosine phosphorylation activity. It is therefore possible that PTPs may prevent or reverse cell transformation and the growth of various cancers by controlling the levels of tyrosine phosphorylation in cells. This hypothesis is supported by studies showing that overexpression of PTPs can suppress transformation in cells, and that specific inhibition of PTPs can enhance cell transformation (Charbonneau, supra).

Phospholipid and Inositol-Phosphate Signaling

Inositol phospholipids (phosphoinositides) are involved in an intracellular signaling pathway that begins with binding of a signaling molecule to a G-protein linked receptor in the plasma membrane. This leads to the phosphorylation of phosphatidylinositol (PI) residues on the inner side of the plasma membrane to the biphosphate state (PIP_2) by inositol kinases. Simultaneously, the G-protein linked receptor binding stimulates a trimeric G-protein which in turn activates a phosphoinositide-specific phospholipase C-β. Phospholipase C-β then cleaves PIP_2 into two products, inositol triphosphate (IP_3) and diacylglycerol. These two products act as mediators for separate signaling events. IP_3 diffuses through the plasma membrane to induce calcium release from the endoplasmic reticulum (ER), while diacylglycerol remains in the membrane and helps activate protein kinase C, an STK that phosphorylates selected proteins in the target cell. The calcium

response initiated by IP_3 is terminated by the dephosphorylation of IP_3 by specific inositol phosphatases. Cellular responses that are mediated by this pathway are glycogen breakdown in the liver in response to vasopressin, smooth muscle contraction in response to acetylcholine, and thrombin-induced platelet aggregation.

Cyclic Nucleotide Signaling

Cyclic nucleotides (cAMP and cGMP) function as intracellular second messengers to transduce a variety of extracellular signals including hormones, light, and neurotransmitters. In particular, cyclic-AMP dependent protein kinases (PKA) are thought to account for all of the effects of cAMP in most mammalian cells, including various hormone-induced cellular responses. Visual excitation and the phototransmission of light signals in the eye is controlled by cyclic-GMP regulated, Ca^{2+}-specific channels. Because of the importance of cellular levels of cyclic nucleotides in mediating these various responses, regulating the synthesis and breakdown of cyclic nucleotides is an important matter. Thus adenylyl cyclase, which synthesizes cAMP from AMP, is activated to increase cAMP levels in muscle by binding of adrenaline to β-andrenergic receptors, while activation of guanylate cyclase and increased cGMP levels in photoreceptors leads to reopening of the Ca^{2+}-specific channels and recovery of the dark state in the eye. In contrast, hydrolysis of cyclic nucleotides by cAMP and cGMP-specific phosphodiesterases (PDEs) produces the opposite of these and other effects mediated by increased cyclic nucleotide levels. PDEs appear to be particularly important in the regulation of cyclic nucleotides, considering the diversity found in this family of proteins. At least seven families of mammalian PDEs (PDE1-7) have been identified based on substrate specificity and affinity, sensitivity to cofactors, and sensitivity to inhibitory drugs (Beavo, J.A. (1995) Physiological Reviews 75:725-48). PDE inhibitors have been found to be particularly useful in treating various clinical disorders. Rolipram, a specific inhibitor of PDE4, has been used in the treatment of depression, and similar inhibitors are undergoing evaluation as anti-inflammatory agents. Theophylline is a nonspecific PDE inhibitor used in the treatment of bronchial asthma and other respiratory diseases (Banner, K.H. and C.P. Page (1995) Eur. Respir. J. 8:996-1000).

G-Protein Signaling

Guanine nucleotide binding proteins (G-proteins) are critical mediators of signal transduction between a particular class of extracellular receptors, the G-protein coupled receptors (GPCR), and intracellular second messengers such as cAMP and Ca^{2+}. G-proteins are linked to the cytosolic side of a GPCR such that activation of the GPCR by ligand binding stimulates binding of the G-protein to GTP, inducing an "active" state in the G-protein. In the active state, the G-protein acts as a signal to trigger other events in the cell such as the increase of cAMP levels or the release of Ca^{2+} into the cytosol from the ER, which, in turn, regulate phosphorylation and activation of other intracellular proteins. Recycling of the G-protein to the inactive state involves hydrolysis of the bound GTP to

GDP by a GTPase activity in the G-protein. (See Alberts, B. et al. (1994) Molecular Biology of the Cell, Garland Publishing, Inc., New York NY, pp.734-759.) Two structurally distinct classes of G-proteins are recognized: heterotrimeric G-proteins, consisting of three different subunits, and monomeric, low molecular weight (LMW), G-proteins consisting of a single polypeptide chain.

The three polypeptide subunits of heterotrimeric G-proteins are the α, β, and γ subunits. The α subunit binds and hydrolyzes GTP. The β and γ subunits form a tight complex that anchors the protein to the inner side of the plasma membrane. The β subunits, also known as G-β proteins or β transducins, contain seven tandem repeats of the WD-repeat sequence motif, a motif found in many proteins with regulatory functions. Mutations and variant expression of β transducin proteins are linked with various disorders (Neer, E.J. et al. (1994) Nature 371:297-300; Margottin, F. et al. (1998) Mol. Cell 1:565-574).

LMW GTP-proteins are GTPases which regulate cell growth, cell cycle control, protein secretion, and intracellular vesicle interaction. They consist of single polypeptides which, like the α subunit of the heterotrimeric G-proteins, are able to bind and hydrolyze GTP, thus cycling between an inactive and an active state. At least sixty members of the LMW G-protein superfamily have been identified and are currently grouped into the six subfamilies of ras, rho, arf, sar1, ran, and rab. Activated ras genes were initially found in human cancers, and subsequent studies confirmed that ras function is critical in determining whether cells continue to grow or become differentiated. Other members of the LMW G-protein superfamily have roles in signal transduction that vary with the function of the activated genes and the locations of the G-proteins.

Guanine nucleotide exchange factors regulate the activities of LMW G-proteins by determining whether GTP or GDP is bound. GTPase-activating protein (GAP) binds to GTP-ras and induces it to hydrolyze GTP to GDP. In contrast, guanine nucleotide releasing protein (GNRP) binds to GDP-ras and induces the release of GDP and the binding of GTP.

Other regulators of G-protein signaling (RGS) also exist that act primarily by negatively regulating the G-protein pathway by an unknown mechanism (Druey, K.M. et al. (1996) Nature 379:742-746). Some 15 members of the RGS family have been identified. RGS family members are related structurally through similarities in an approximately 120 amino acid region termed the RGS domain and functionally by their ability to inhibit the interleukin (cytokine) induction of MAP kinase in cultured mammalian 293T cells (Druey, supra).

Calcium Signaling Molecules

Ca^{+2} is another second messenger molecule that is even more widely used as an intracellular mediator than cAMP. Two pathways exist by which Ca^{+2} can enter the cytosol in response to extracellular signals: One pathway acts primarily in nerve signal transduction where Ca^{+2} enters a

nerve terminal through a voltage-gated Ca^{+2} channel. The second is a more ubiquitous pathway in which Ca^{+2} is released from the ER into the cytosol in response to binding of an extracellular signaling molecule to a receptor. Ca^{2+} directly activates regulatory enzymes, such as protein kinase C, which trigger signal transduction pathways. Ca^{2+} also binds to specific Ca^{2+}-binding proteins (CBPs) such as calmodulin (CaM) which then activate multiple target proteins in the cell including enzymes, membrane transport pumps, and ion channels. CaM interactions are involved in a multitude of cellular processes including, but not limited to, gene regulation, DNA synthesis, cell cycle progression, mitosis, cytokinesis, cytoskeletal organization, muscle contraction, signal transduction, ion homeostasis, exocytosis, and metabolic regulation (Celio, M.R. et al. (1996) Guidebook to Calcium-binding Proteins, Oxford University Press, Oxford, UK, pp. 15-20). Some CBPs can serve as a storage depot for Ca^{2+} in an inactive state. Calsequestrin is one such CBP that is expressed in isoforms specific to cardiac muscle and skeletal muscle. It is suggested that calsequestrin binds Ca^{2+} in a rapidly exchangeable state that is released during Ca^{2+} -signaling conditions (Celio, M.R. et al. (1996) Guidebook to Calcium-binding Proteins, Oxford University Press, New York NY, pp. 222-224).

Cyclins

Cell division is the fundamental process by which all living things grow and reproduce. In most organisms, the cell cycle consists of three principle steps; interphase, mitosis, and cytokinesis. Interphase, involves preparations for cell division, replication of the DNA and production of essential proteins. In mitosis, the nuclear material is divided and separates to opposite sides of the cell. Cytokinesis is the final division and fission of the cell cytoplasm to produce the daughter cells.

The entry and exit of a cell from mitosis is regulated by the synthesis and destruction of a family of activating proteins called cyclins. Cyclins act by binding to and activating a group of cyclin-dependent protein kinases (Cdks) which then phosphorylate and activate selected proteins involved in the mitotic process. Several types of cyclins exist. (Ciechanover, A. (1994) Cell 79:13-21.) Two principle types are mitotic cyclin, or cyclin B, which controls entry of the cell into mitosis, and G1 cyclin, which controls events that drive the cell out of mitosis.

Signal Complex Scaffolding Proteins

Ceretain proteins in intracellular signaling pathways serve to link or cluster other proteins involved in the signaling cascade. A conserved protein domain called the PDZ domain has been identified in various membrane-associated signaling proteins. This domain has been implicated in receptor and ion channel clustering and in the targeting of multiprotein signaling complexes to specialized functional regions of the cytosolic face of the plasma membrane. (For a review of PDZ domain-containing proteins, see Ponting, C.P. et al. (1997) Bioessays 19:469-479.) A large

proportion of PDZ domains are found in the eukaryotic MAGUK (membrane-associated guanylate kinase) protein family, members of which bind to the intracellular domains of receptors and channels. However, PDZ domains are also found in diverse membrane-localized proteins such as protein tyrosine phosphatases, serine/threonine kinases, G-protein cofactors, and synapse-associated proteins such as syntrophins and neuronal nitric oxide synthase (nNOS). Generally, about one to three PDZ domains are found in a given protein, although up to nine PDZ domains have been identified in a single protein.

Membrane Transport Molecules

The plasma membrane acts as a barrier to most molecules. Transport between the cytoplasm and the extracellular environment, and between the cytoplasm and lumenal spaces of cellular organelles requires specific transport proteins. Each transport protein carries a particular class of molecule, such as ions, sugars, or amino acids, and often is specific to a certain molecular species of the class. A variety of human inherited diseases are caused by a mutation in a transport protein. For example, cystinuria is an inherited disease that results from the inability to transport cystine, the disulfide-linked dimer of cysteine, from the urine into the blood. Accumulation of cystine in the urine leads to the formation of cystine stones in the kidneys.

Transport proteins are multi-pass transmembrane proteins, which either actively transport molecules across the membrane or passively allow them to cross. Active transport involves directional pumping of a solute across the membrane, usually against an electrochemical gradient. Active transport is tightly coupled to a source of metabolic energy, such as ATP hydrolysis or an electrochemically favorable ion gradient. Passive transport involves the movement of a solute down its electrochemical gradient. Transport proteins can be further classified as either carrier proteins or channel proteins. Carrier proteins, which can function in active or passive transport, bind to a specific solute to be transported and undergo a conformational change which transfers the bound solute across the membrane. Channel proteins, which only function in passive transport, form hydrophilic pores across the membrane. When the pores open, specific solutes, such as inorganic ions, pass through the membrane and down the electrochemical gradient of the solute.

Carrier proteins which transport a single solute from one side of the membrane to the other are called uniporters. In contrast, coupled transporters link the transfer of one solute with simultaneous or sequential transfer of a second solute, either in the same direction (symport) or in the opposite direction (antiport). For example, intestinal and kidney epithelium contains a variety of symporter systems driven by the sodium gradient that exists across the plasma membrane. Sodium moves into the cell down its electrochemical gradient and brings the solute into the cell with it. The sodium gradient that provides the driving force for solute uptake is maintained by the ubiquitous

Na^{+}/K^{+} ATPase. Sodium-coupled transporters include the mammalian glucose transporter (SGLT1), iodide transporter (NIS), and multivitamin transporter (SMVT). All three transporters have twelve putative transmembrane segments, extracellular glycosylation sites, and cytoplasmically-oriented N- and C-termini. NIS plays a crucial role in the evaluation, diagnosis, and treatment of various thyroid pathologies because it is the molecular basis for radioiodide thyroid-imaging techniques and for specific targeting of radioisotopes to the thyroid gland (Levy, O. et al. (1997) Proc. Natl. Acad. Sci. USA 94:5568-5573). SMVT is expressed in the intestinal mucosa, kidney, and placenta, and is implicated in the transport of the water-soluble vitamins, e.g., biotin and pantothenate (Prasad, P.D. et al. (1998) J. Biol. Chem. 273:7501-7506).

Transporters play a major role in the regulation of pH, excretion of drugs, and the cellular K^{+}/Na^{+} balance. Monocarboxylate anion transporters are proton-coupled symporters with a broad substrate specificity that includes L-lactate, pyruvate, and the ketone bodies acetate, acetoacetate, and beta-hydroxybutyrate. At least seven isoforms have been identified to date. The isoforms are predicted to have twelve transmembrane (TM) helical domains with a large intracellular loop between TM6 and TM7, and play a critical role in maintaining intracellular pH by removing the protons that are produced stoichiometrically with lactate during glycolysis. The best characterized H(+)-monocarboxylate transporter is that of the erythrocyte membrane, which transports L-lactate and a wide range of other aliphatic monocarboxylates. Other cells possess H(+)-linked monocarboxylate transporters with differing substrate and inhibitor selectivities. In particular, cardiac muscle and tumor cells have transporters that differ in their K_m values for certain substrates, including stereoselectivity for L- over D-lactate, and in their sensitivity to inhibitors. There are Na(+)-monocarboxylate cotransporters on the luminal surface of intestinal and kidney epithelia, which allow the uptake of lactate, pyruvate, and ketone bodies in these tissues. In addition, there are specific and selective transporters for organic cations and organic anions in organs including the kidney, intestine and liver. Organic anion transporters are selective for hydrophobic, charged molecules with electron-attracting side groups. Organic cation transporters, such as the ammonium transporter, mediate the secretion of a variety of drugs and endogenous metabolites, and contribute to the maintenance of intercellular pH. (Poole, R.C. and A.P. Halestrap (1993) Am. J. Physiol. 264:C761-C782; Price, N.T. et al. (1998) Biochem. J. 329:321-328; and Martinelle, K. and I. Haggstrom (1993) J. Biotechnol. 30: 339-350.)

The largest and most diverse family of transport proteins known is the ATP-binding cassette (ABC) transporters. As a family, ABC transporters can transport substances that differ markedly in chemical structure and size, ranging from small molecules such as ions, sugars, amino acids, peptides, and phospholipids, to lipopeptides, large proteins, and complex hydrophobic drugs. ABC proteins consist of four modules: two nucleotide-binding domains (NBD), which hydrolyze ATP to supply the

energy required for transport, and two membrane-spanning domains (MSD), each containing six putative transmembrane segments. These four modules may be encoded by a single gene, as is the case for the cystic fibrosis transmembrane regulator (CFTR), or by separate genes. When encoded by separate genes, each gene product contains a single NBD and MSD. These "half-molecules" form homo- and heterodimers, such as Tap1 and Tap2, the endoplasmic reticulum-based major histocompatibility (MHC) peptide transport system. Several genetic diseases are attributed to defects in ABC transporters, such as the following diseases and their corresponding proteins: cystic fibrosis (CFTR, an ion channel), adrenoleukodystrophy (adrenoleukodystrophy protein, ALDP), Zellweger syndrome (peroxisomal membrane protein-70, PMP70), and hyperinsulinemic hypoglycemia (sulfonylurea receptor, SUR). Overexpression of the multidrug resistance (MDR) protein, another ABC transporter, in human cancer cells makes the cells resistant to a variety of cytotoxic drugs used in chemotherapy (Taglight, D. and S. Michaelis (1998) Meth. Enzymol. 292:131-163).

Transport of fatty acids across the plasma membrane can occur by diffusion, a high capacity, low affinity process. However, under normal physiological conditions a significant fraction of fatty acid transport appears to occur via a high affinity, low capacity protein-mediated transport process. Fatty acid transport protein (FATP), an integral membrane protein with four transmembrane segments, is expressed in tissues exhibiting high levels of plasma membrane fatty acid flux, such as muscle, heart, and adipose. Expression of FATP is upregulated in 3T3-L1 cells during adipose conversion, and expression in COS7 fibroblasts elevates uptake of long-chain fatty acids (Hui, T.Y. et al. (1998) J. Biol. Chem. 273:27420-27429).

Ion Channels

The electrical potential of a cell is generated and maintained by controlling the movement of ions across the plasma membrane. The movement of ions requires ion channels, which form an ion-selective pore within the membrane. There are two basic types of ion channels, ion transporters and gated ion channels. Ion transporters utilize the energy obtained from ATP hydrolysis to actively transport an ion against the ion's concentration gradient. Gated ion channels allow passive flow of an ion down the ion's electrochemical gradient under restricted conditions. Together, these types of ion channels generate, maintain, and utilize an electrochemical gradient that is used in 1) electrical impulse conduction down the axon of a nerve cell, 2) transport of molecules into cells against concentration gradients, 3) initiation of muscle contraction, and 4) endocrine cell secretion.

Ion transporters generate and maintain the resting electrical potential of a cell. Utilizing the energy derived from ATP hydrolysis, they transport ions against the ion's concentration gradient. These transmembrane ATPases are divided into three families. The phosphorylated (P) class ion transporters, including Na^+-K^+ ATPase, Ca^{2+}-ATPase, and H^+-ATPase, are activated by a

phosphorylation event. P-class ion transporters are responsible for maintaining resting potential distributions such that cytosolic concentrations of Na^+ and Ca^{2+} are low and cytosolic concentration of K^+ is high. The vacuolar (V) class of ion transporters includes H^+ pumps on intracellular organelles, such as lysosomes and Golgi. V-class ion transporters are responsible for generating the low pH within the lumen of these organelles that is required for function. The coupling factor (F) class consists of H^+ pumps in the mitochondria. F-class ion transporters utilize a proton gradient to generate ATP from ADP and inorganic phosphate (P_i).

The resting potential of the cell is utilized in many processes involving carrier proteins and gated ion channels. Carrier proteins utilize the resting potential to transport molecules into and out of the cell. Amino acid and glucose transport into many cells is linked to sodium ion co-transport (symport) so that the movement of Na^+ down an electrochemical gradient drives transport of the other molecule up a concentration gradient. Similarly, cardiac muscle links transfer of Ca^{2+} out of the cell with transport of Na^+ into the cell (antiport).

Ion channels share common structural and mechanistic themes. The channel consists of four or five subunits or protein monomers that are arranged like a barrel in the plasma membrane. Each subunit typically consists of six potential transmembrane segments (S1, S2, S3, S4, S5, and S6). The center of the barrel forms a pore lined by α-helices or β-strands. The side chains of the amino acid residues comprising the α-helices or β-strands establish the charge (cation or anion) selectivity of the channel. The degree of selectivity, or what specific ions are allowed to pass through the channel, depends on the diameter of the narrowest part of the pore.

Gated ion channels control ion flow by regulating the opening and closing of pores. These channels are categorized according to the manner of regulating the gating function. Mechanically-gated channels open pores in response to mechanical stress, voltage-gated channels open pores in response to changes in membrane potential, and ligand-gated channels open pores in the presence of a specific ion, nucleotide, or neurotransmitter.

Voltage-gated Na^+ and K^+ channels are necessary for the function of electrically excitable cells, such as nerve and muscle cells. Action potentials, which lead to neurotransmitter release and muscle contraction, arise from large, transient changes in the permeability of the membrane to Na^+ and K^+ ions. Depolarization of the membrane beyond the threshold level opens voltage-gated Na^+ channels. Sodium ions flow into the cell, further depolarizing the membrane and opening more voltage-gated Na^+ channels, which propagates the depolarization down the length of the cell. Depolarization also opens voltage-gated potassium channels. Consequently, potassium ions flow outward, which leads to repolarization of the membrane. Voltage-gated channels utilize charged residues in the fourth transmembrane segment (S4) to sense voltage change. The open state lasts only about 1 millisecond, at

which time the channel spontaneously converts into an inactive state that cannot be opened irrespective of the membrane potential. Inactivation is mediated by the channel's N-terminus, which acts as a plug that closes the pore. The transition from an inactive to a closed state requires a return to resting potential.

Voltage-gated Na^+ channels are heterotrimeric complexes composed of a 260 kDa pore forming α subunit that associates with two smaller auxiliary subunits, $\beta1$ and $\beta2$. The $\beta2$ subunit is an integral membrane glycoprotein that contains an extracellular Ig domain, and its association with α and $\beta1$ subunits correlates with increased functional expression of the channel, a change in its gating properties, and an increase in whole cell capacitance due to an increase in membrane surface area. (Isom, L.L. et al. (1995) Cell 83:433-442.)

Voltage-gated Ca^{2+} channels are involved in presynaptic neurotransmitter release, and heart and skeletal muscle contraction. The voltage-gated Ca^{2+} channels from skeletal muscle (L-type) and brain (N-type) have been purified, and though their functions differ dramatically, they have similar subunit compositions. The channels are composed of three subunits. The α_1 subunit forms the membrane pore and voltage sensor, while the $\alpha_2\delta$ and β subunits modulate the voltage-dependence, gating properties, and the current amplitude of the channel. These subunits are encoded by at least six α_1, one $\alpha_2\delta$, and four β genes. A fourth subunit, γ, has been identified in skeletal muscle. (Walker, D. et al. (1998) J. Biol. Chem. 273:2361-2367; and Jay, S.D. et al. (1990) Science 248:490-492.)

Chloride channels are necessary in endocrine secretion and in regulation of cytosolic and organelle pH. In secretory epithelial cells, Cl^- enters the cell across a basolateral membrane through an Na^+, K^+/Cl^- cotransporter, accumulating in the cell above its electrochemical equilibrium concentration. Secretion of Cl^- from the apical surface, in response to hormonal stimulation, leads to flow of Na^+ and water into the secretory lumen. The cystic fibrosis transmembrane conductance regulator (CFTR) is a chloride channel encoded by the gene for cystic fibrosis, a common fatal genetic disorder in humans. Loss of CFTR function decreases transepithelial water secretion and, as a result, the layers of mucus that coat the respiratory tree, pancreatic ducts, and intestine are dehydrated and difficult to clear. The resulting blockage of these sites leads to pancreatic insufficiency, "meconium ileus", and devastating "chronic obstructive pulmonary disease" (Al-Awqati, Q. et al. (1992) J. Exp. Biol. 172:245-266).

Many intracellular organelles contain H^+-ATPase pumps that generate transmembrane pH and electrochemical differences by moving protons from the cytosol to the organelle lumen. If the membrane of the organelle is permeable to other ions, then the electrochemical gradient can be abrogated without affecting the pH differential. In fact, removal of the electrochemical barrier allows more H^+ to be pumped across the membrane, increasing the pH differential. Cl^- is the sole counterion of H^+ translocation in a number of organelles, including chromaffin granules, Golgi vesicles,

lysosomes, and endosomes. Functions that require a low vacuolar pH include uptake of small molecules such as biogenic amines in chromaffin granules, processing of vacuolar constituents such as pro-hormones by proteolytic enzymes, and protein degradation in lysosomes (Al-Awqati, supra).

Ligand-gated channels open their pores when an extracellular or intracellular mediator binds to the channel. Neurotransmitter-gated channels are channels that open when a neurotransmitter binds to their extracellular domain. These channels exist in the postsynaptic membrane of nerve or muscle cells. There are two types of neurotransmitter-gated channels. Sodium channels open in response to excitatory neurotransmitters, such as acetylcholine, glutamate, and serotonin. This opening causes an influx of Na^+ and produces the initial localized depolarization that activates the voltage-gated channels and starts the action potential. Chloride channels open in response to inhibitory neurotransmitters, such as γ-aminobutyric acid (GABA) and glycine, leading to hyperpolarization of the membrane and the subsequent generation of an action potential.

Ligand-gated channels can be regulated by intracellular second messengers. Calcium-activated K^+ channels are gated by internal calcium ions. In nerve cells, an influx of calcium during depolarization opens K^+ channels to modulate the magnitude of the action potential (Ishi, T.M. et al. (1997) Proc. Natl. Acad. Sci. USA 94:11651-11656). Cyclic nucleotide-gated (CNG) channels are gated by cytosolic cyclic nucleotides. The best examples of these are the cAMP-gated Na^+ channels involved in olfaction and the cGMP-gated cation channels involved in vision. Both systems involve ligand-mediated activation of a G-protein coupled receptor which then alters the level of cyclic nucleotide within the cell.

Ion channels are expressed in a number of tissues where they are implicated in a variety of processes. CNG channels, while abundantly expressed in photoreceptor and olfactory sensory cells, are also found in kidney, lung, pineal, retinal ganglion cells, testis, aorta, and brain. Calcium-activated K^+ channels may be responsible for the vasodilatory effects of bradykinin in the kidney and for shunting excess K^+ from brain capillary endothelial cells into the blood. They are also implicated in repolarizing granulocytes after agonist-stimulated depolarization (Ishi, supra). Ion channels have been the target for many drug therapies. Neurotransmitter-gated channels have been targeted in therapies for treatment of insomnia, anxiety, depression, and schizophrenia. Voltage-gated channels have been targeted in therapies for arrhythmia, ischemic stroke, head trauma, and neurodegenerative disease (Taylor, C.P. and L.S. Narasimhan (1997) Adv. Pharmacol. 39:47-98).

Disease Correlation

The etiology of numerous human diseases and disorders can be attributed to defects in the transport of molecules across membranes. Defects in the trafficking of membrane-bound transporters and ion channels are associated with several disorders, e.g. cystic fibrosis, glucose-galactose

malabsorption syndrome, hypercholesterolemia, von Gierke disease, and certain forms of diabetes mellitus. Single-gene defect diseases resulting in an inability to transport small molecules across membranes include, e.g., cystinuria, iminoglycinuria, Hartup disease, and Fanconi disease (van't Hoff, W.G. (1996) Exp. Nephrol. 4:253-262; Talente, G.M. et al. (1994) Ann. Intern. Med. 120:218-226; and Chillon, M. et al. (1995) New Engl. J. Med. 332:1475-1480).

Protein Modification and Maintenance Molecules

SEQ ID NO:34 encodes, for example, a protein modification and maintenance molecule.

The cellular processes regulating modification and maintenance of protein molecules coordinate their conformation, stabilization, and degradation. Each of these processes is mediated by key enzymes or proteins such as proteases, protease inhibitors, transferases, isomerases, and molecular chaperones.

Proteases

Proteases cleave proteins and peptides at the peptide bond that forms the backbone of the peptide and protein chain. Proteolytic processing is essential to cell growth, differentiation, remodeling, and homeostasis as well as inflammation and immune response. Typical protein half-lives range from hours to a few days, so that within all living cells, precursor proteins are being cleaved to their active form, signal sequences proteolytically removed from targeted proteins, and aged or defective proteins degraded by proteolysis. Proteases function in bacterial, parasitic, and viral invasion and replication within a host. Four principal categories of mammalian proteases have been identified based on active site structure, mechanism of action, and overall three-dimensional structure. (Beynon, R.J. and J.S. Bond (1994) Proteolytic Enzymes: A Practical Approach, Oxford University Press, New York NY, pp. 1-5).

The serine proteases (SPs) have a serine residue, usually within a conserved sequence, in an active site composed of the serine, an aspartate, and a histidine residue. SPs include the digestive enzymes trypsin and chymotrypsin, components of the complement cascade and the blood-clotting cascade, and enzymes that control extracellular protein degradation. The main SP sub-families are trypases, which cleave after arginine or lysine; aspartases, which cleave after aspartate; chymases, which cleave after phenylalanine or leucine; metases, which cleavage after methionine; and serases which cleave after serine. Enterokinase, the initiator of intestinal digestion, is a serine protease found in the intestinal brush border, where it cleaves the acidic propeptide from trypsinogen to yield active trypsin (Kitamoto, Y. et al. (1994) Proc. Natl. Acad. Sci. USA 91:7588-7592). Prolylcarboxypeptidase, a lysosomal serine peptidase that cleaves peptides such as angiotensin II and III and [des-Arg9] bradykinin, shares sequence homology with members of both the serine

carboxypeptidase and prolylendopeptidase families (Tan, F. et al. (1993) J. Biol. Chem. 268:16631-16638).

Cysteine proteases (CPs) have a cysteine as the major catalytic residue at an active site where catalysis proceeds via an intermediate thiol ester and is facilitated by adjacent histidine and aspartic acid residues. CPs are involved in diverse cellular processes ranging from the processing of precursor proteins to intracellular degradation. Mammalian CPs include lysosomal cathepsins and cytosolic calcium activated proteases, calpains. CPs are produced by monocytes, macrophages and other cells of the immune system which migrate to sites of inflammation and secrete molecules involved in tissue repair. Overabundance of these repair molecules plays a role in certain disorders. In autoimmune diseases such as rheumatoid arthritis, secretion of the cysteine peptidase cathepsin C degrades collagen, laminin, elastin and other structural proteins found in the extracellular matrix of bones.

Aspartic proteases are members of the cathepsin family of lysosomal proteases and include pepsin A, gastricsin, chymosin, renin, and cathepsins D and E. Aspartic proteases have a pair of aspartic acid residues in the active site, and are most active in the pH 2 - 3 range, in which one of the aspartate residues is ionized, the other un-ionized. Aspartic proteases include bacterial penicillopepsin, mammalian pepsin, renin, chymosin, and certain fungal proteases. Abnormal regulation and expression of cathepsins is evident in various inflammatory disease states. In cells isolated from inflamed synovia, the mRNA for stromelysin, cytokines, TIMP-1, cathepsin, gelatinase, and other molecules is preferentially expressed. Expression of cathepsins L and D is elevated in synovial tissues from patients with rheumatoid arthritis and osteoarthritis. Cathepsin L expression may also contribute to the influx of mononuclear cells which exacerbates the destruction of the rheumatoid synovium. (Keyszer, G.M. (1995) Arthritis Rheum. 38:976-984.) The increased expression and differential regulation of the cathepsins are linked to the metastatic potential of a variety of cancers and as such are of therapeutic and prognostic interest (Chambers, A.F. et al. (1993) Crit. Rev. Oncog. 4:95-114).

Metalloproteases have active sites that include two glutamic acid residues and one histidine residue that serve as binding sites for zinc. Carboxypeptidases A and B are the principal mammalian metalloproteases. Both are exoproteases of similar structure and active sites. Carboxypeptidase A, like chymotrypsin, prefers C-terminal aromatic and aliphatic side chains of hydrophobic nature, whereas carboxypeptidase B is directed toward basic arginine and lysine residues. Glycoprotease (GCP), or O-sialoglycoprotein endopeptidase, is a metallopeptidase which specifically cleaves O-sialoglycoproteins such as glycophorin A. Another metallopeptidase, placental leucine aminopeptidase (P-LAP) degrades several peptide hormones such as oxytocin and vasopressin,

suggesting a role in maintaining homeostasis during pregnancy, and is expressed in several tissues (Rogi, T. et al. (1996) J. Biol. Chem. 271:56-61).

Ubiquitin proteases are associated with the ubiquitin conjugation system (UCS), a major pathway for the degradation of cellular proteins in eukaryotic cells and some bacteria. The UCS mediates the elimination of abnormal proteins and regulates the half-lives of important regulatory proteins that control cellular processes such as gene transcription and cell cycle progression. In the UCS pathway, proteins targeted for degradation are conjugated to a ubiquitin, a small heat stable protein. The ubiquitinated protein is then recognized and degraded by proteasome, a large, multisubunit proteolytic enzyme complex, and ubiquitin is released for reutilization by ubiquitin protease. The UCS is implicated in the degradation of mitotic cyclic kinases, oncoproteins, tumor suppressor genes such as p53, viral proteins, cell surface receptors associated with signal transduction, transcriptional regulators, and mutated or damaged proteins (Ciechanover, A. (1994) Cell 79:13-21). A murine proto-oncogene, Unp, encodes a nuclear ubiquitin protease whose overexpression leads to oncogenic transformation of NIH3T3 cells, and the human homolog of this gene is consistently elevated in small cell tumors and adenocarcinomas of the lung (Gray, D.A. (1995) Oncogene 10:2179-2183).

Signal Peptidases

The mechanism for the translocation process into the endoplasmic reticulum (ER) involves the recognition of an N-terminal signal peptide on the elongating protein. The signal peptide directs the protein and attached ribosome to a receptor on the ER membrane. The polypeptide chain passes through a pore in the ER membrane into the lumen while the N-terminal signal peptide remains attached at the membrane surface. The process is completed when signal peptidase located inside the ER cleaves the signal peptide from the protein and releases the protein into the lumen.

Protease Inhibitors

Protease inhibitors and other regulators of protease activity control the activity and effects of proteases. Protease inhibitors have been shown to control pathogenesis in animal models of proteolytic disorders (Murphy, G. (1991) Agents Actions Suppl. 35:69-76). Low levels of the cystatins, low molecular weight inhibitors of the cysteine proteases, correlate with malignant progression of tumors. (Calkins, C. et al (1995) Biol. Biochem. Hoppe Seyler 376:71-80). Serpins are inhibitors of mammalian plasma serine proteases. Many serpins serve to regulate the blood clotting cascade and/or the complement cascade in mammals. Sp32 is a positive regulator of the mammalian acrosomal protease, acrosin, that binds the proenzyme, proacrosin, and thereby aides in packaging the enzyme into the acrosomal matrix (Baba, T. et al. (1994) J. Biol. Chem. 269:10133-10140). The Kunitz family of serine protease inhibitors are characterized by one or more "Kunitz domains" containing a series of cysteine residues that are regularly spaced over approximately 50

amino acid residues and form three intrachain disulfide bonds. Members of this family include aprotinin, tissue factor pathway inhibitor (TFPI-1 and TFPI-2), inter-α-trypsin inhibitor, and bikunin. (Marlor, C.W. et al. (1997) J. Biol. Chem. 272:12202-12208.) Members of this family are potent inhibitors (in the nanomolar range) against serine proteases such as kallikrein and plasmin. Aprotinin has clinical utility in reduction of perioperative blood loss.

A major portion of all proteins synthesized in eukaryotic cells are synthesized on the cytosolic surface of the endoplasmic reticulum (ER). Before these immature proteins are distributed to other organelles in the cell or are secreted, they must be transported into the interior lumen of the ER where post-translational modifications are performed. These modifications include protein folding and the formation of disulfide bonds, and N-linked glycosylations.

Protein Isomerases

Protein folding in the ER is aided by two principal types of protein isomerases, protein disulfide isomerase (PDI), and peptidyl-prolyl isomerase (PPI). PDI catalyzes the oxidation of free sulfhydryl groups in cysteine residues to form intramolecular disulfide bonds in proteins. PPI, an enzyme that catalyzes the isomerization of certain proline imidic bonds in oligopeptides and proteins, is considered to govern one of the rate limiting steps in the folding of many proteins to their final functional conformation. The cyclophilins represent a major class of PPI that was originally identified as the major receptor for the immunosuppressive drug cyclosporin A (Handschumacher, R.E. et al. (1984) Science 226: 544-547).

Protein Glycosylation

The glycosylation of most soluble secreted and membrane-bound proteins by oligosaccharides linked to asparagine residues in proteins is also performed in the ER. This reaction is catalyzed by a membrane-bound enzyme, oligosaccharyl transferase. Although the exact purpose of this "N-linked" glycosylation is unknown, the presence of oligosaccharides tends to make a glycoprotein resistant to protease digestion. In addition, oligosaccharides attached to cell-surface proteins called selectins are known to function in cell-cell adhesion processes (Alberts, B. et al. (1994) Molecular Biology of the Cell, Garland Publishing Co., New York NY, p.608). "O-linked" glycosylation of proteins also occurs in the ER by the addition of N-acetylgalactosamine to the hydroxyl group of a serine or threonine residue followed by the sequential addition of other sugar residues to the first. This process is catalysed by a series of glycosyltransferases each specific for a particular donor sugar nucleotide and acceptor molecule (Lodish, H. et al. (1995) Molecular Cell Biology, W.H. Freeman and Co., New York NY, pp.700-708). In many cases, both N- and O-linked oligosaccharides appear to be required for the secretion of proteins or the movement of plasma membrane glycoproteins to the cell surface.

An additional glycosylation mechanism operates in the ER specifically to target lysosomal enzymes to lysosomes and prevent their secretion. Lysosomal enzymes in the ER receive an N-linked oligosaccharide, like plasma membrane and secreted proteins, but are then phosphorylated on one or two mannose residues. The phosphorylation of mannose residues occurs in two steps, the first step being the addition of an N-acetylglucosamine phosphate residue by N-acetylglucosamine phosphotransferase, and the second the removal of the N-acetylglucosamine group by phosphodiesterase. The phosphorylated mannose residue then targets the lysosomal enzyme to a mannose 6-phosphate receptor which transports it to a lysosome vesicle (Lodish, supra, pp. 708-711).

Chaperones

Molecular chaperones are proteins that aid in the proper folding of immature proteins and refolding of improperly folded ones, the assembly of protein subunits, and in the transport of unfolded proteins across membranes. Chaperones are also called heat-shock proteins (hsp) because of their tendency to be expressed in dramatically increased amounts following brief exposure of cells to elevated temperatures. This latter property most likely reflects their need in the refolding of proteins that have become denatured by the high temperatures. Chaperones may be divided into several classes according to their location, function, and molecular weight, and include hsp60, TCP1, hsp70, hsp40 (also called DnaJ), and hsp90. For example, hsp90 binds to steroid hormone receptors, represses transcription in the absence of the ligand, and provides proper folding of the ligand-binding domain of the receptor in the presence of the hormone (Burston, S.G. and A.R. Clarke (1995) Essays Biochem. 29:125-136). Hsp60 and hsp70 chaperones aid in the transport and folding of newly synthesized proteins. Hsp70 acts early in protein folding, binding a newly synthesized protein before it leaves the ribosome and transporting the protein to the mitochondria or ER before releasing the folded protein. Hsp60, along with hsp10, binds misfolded proteins and gives them the opportunity to refold correctly. All chaperones share an affinity for hydrophobic patches on incompletely folded proteins and the ability to hydrolyze ATP. The energy of ATP hydrolysis is used to release the hsp-bound protein in its properly folded state (Alberts, supra, pp 214, 571-572).

Nucleic Acid Synthesis and Modification Molecules

SEQ ID NO:35 and SEQ ID NO:36 encode, for example, nucleic acid synthesis and modification molecules.

Polymerases

DNA and RNA replication are critical processes for cell replication and function. DNA and RNA replication are mediated by the enzymes DNA and RNA polymerase, respectively, by a "templating" process in which the nucleotide sequence of a DNA or RNA strand is copied by complementary base-pairing into a complementary nucleic acid sequence of either DNA or RNA.

However, there are fundamental differences between the two processes.

DNA polymerase catalyzes the stepwise addition of a deoxyribonucleotide to the 3'-OH end of a polynucleotide strand (the primer strand) that is paired to a second (template) strand. The new DNA strand therefore grows in the 5' to 3' direction (Alberts, B. et al. (1994)The Molecular Biology of the Cell, Garland Publishing Inc., New York NY, pp. 251-254). The substrates for the polymerization reaction are the corresponding deoxynucleotide triphosphates which must base-pair with the correct nucleotide on the template strand in order to be recognized by the polymerase. Because DNA exists as a double-stranded helix, each of the two strands may serve as a template for the formation of a new complementary strand. Each of the two daughter cells of the dividing cell therefore inherits a new DNA double helix containing one old and one new strand. Thus, DNA is said to be replicated "semiconservatively" by DNA polymerase. In addition to the synthesis of new DNA, DNA polymerase is also involved in the repair of damaged DNA as discussed below under "Ligases."

In contrast to DNA polymerase, RNA polymerase uses a DNA template strand to "transcribe" DNA into RNA using ribonucleotide triphosphates as substrates. Like DNA polymerization, RNA polymerization proceeds in a 5' to 3' direction by addition of a ribonucleoside monophosphate to the 3'-OH end of a growing RNA chain. DNA transcription generates messenger RNAs (mRNA) that carry information for protein synthesis, as well as the transfer, ribosomal, and other RNAs that have structural or catalytic functions. In eukaryotes, three discrete RNA polymerases synthesize the three different types of RNA (Alberts, supra, pp. 367-368). RNA polymerase I makes the large ribosomal RNAs, RNA polymerase II makes the mRNAs that will be translated into proteins, and RNA polymerase III makes a variety of small, stable RNAs, including 5S ribosomal RNA and the transfer RNAs (tRNA). In all cases, RNA synthesis is initiated by binding of the RNA polymerase to a promoter region on the DNA and synthesis begins at a start site within the promoter. Synthesis is completed at a broad, general stop or termination region in the DNA where both the polymerase and the completed RNA chain are released.

Ligases

DNA repair is the process by which accidental base changes, such as those produced by oxidative damage, hydrolytic attack, or uncontrolled methylation of DNA are corrected before replication or transcription of the DNA can occur. Because of the efficiency of the DNA repair process, fewer than one in one thousand accidental base changes causes a mutation (Alberts, supra, pp. 245-249). The three steps common to most types of DNA repair are (1) excision of the damaged or altered base or nucleotide by DNA nucleases, leaving a gap; (2) insertion of the correct nucleotide in this gap by DNA polymerase using the complementary strand as the template; and (3) sealing the break left between the inserted nucleotide(s) and the existing DNA strand by DNA ligase. In the last

reaction, DNA ligase uses the energy from ATP hydrolysis to activate the 5' end of the broken phosphodiester bond before forming the new bond with the 3'-OH of the DNA strand. In Bloom's syndrome, an inherited human disease, individuals are partially deficient in DNA ligation and consequently have an increased incidence of cancer (Alberts, supra, p. 247).

Nucleases

Nucleases comprise both enzymes that hydrolyze DNA (DNase) and RNA (RNase). They serve different purposes in nucleic acid metabolism. Nucleases hydrolyze the phosphodiester bonds between adjacent nucleotides either at internal positions (endonucleases) or at the terminal 3' or 5' nucleotide positions (exonucleases). A DNA exonuclease activity in DNA polymerase, for example, serves to remove improperly paired nucleotides attached to the 3'-OH end of the growing DNA strand by the polymerase and thereby serves a "proofreading" function. As mentioned above, DNA endonuclease activity is involved in the excision step of the DNA repair process.

RNases also serve a variety of functions. For example, RNase P is a ribonucleoprotein enzyme which cleaves the 5' end of pre-tRNAs as part of their maturation process. RNase H digests the RNA strand of an RNA/DNA hybrid. Such hybrids occur in cells invaded by retroviruses, and RNase H is an important enzyme in the retroviral replication cycle. Pancreatic RNase secreted by the pancreas into the intestine hydrolyzes RNA present in ingested foods. RNase activity in serum and cell extracts is elevated in a variety of cancers and infectious diseases (Schein, C.H. (1997) Nat. Biotechnol. 15:529-536). Regulation of RNase activity is being investigated as a means to control tumor angiogenesis, allergic reactions, viral infection and replication, and fungal infections.

Methylases

Methylation of specific nucleotides occurs in both DNA and RNA, and serves different functions in the two macromolecules. Methylation of cytosine residues to form 5-methyl cytosine in DNA occurs specifically at CG sequences which are base-paired with one another in the DNA double-helix. This pattern of methylation is passed from generation to generation during DNA replication by an enzyme called "maintenance methylase" that acts preferentially on those CG sequences that are base-paired with a CG sequence that is already methylated. Such methylation appears to distinguish active from inactive genes by preventing the binding of regulatory proteins that "turn on" the gene, but permit the binding of proteins that inactivate the gene (Alberts, supra, pp. 448-451). In RNA metabolism, "tRNA methylase" produces one of several nucleotide modifications in tRNA that affect the conformation and base-pairing of the molecule and facilitate the recognition of the appropriate mRNA codons by specific tRNAs. The primary methylation pattern is the dimethylation of guanine residues to form N,N-dimethyl guanine.

Helicases and Single-Stranded Binding Proteins

Helicases are enzymes that destabilize and unwind double helix structures in both DNA and

RNA. Since DNA replication occurs more or less simultaneously on both strands, the two strands must first separate to generate a replication "fork" for DNA polymerase to act on. Two types of replication proteins contribute to this process, DNA helicases and single-stranded binding proteins. DNA helicases hydrolyze ATP and use the energy of hydrolysis to separate the DNA strands. Single-stranded binding proteins (SSBs) then bind to the exposed DNA strands without covering the bases, thereby temporarily stabilizing them for templating by the DNA polymerase (Alberts, supra, pp. 255-256).

RNA helicases also alter and regulate RNA conformation and secondary structure. Like the DNA helicases, RNA helicases utilize energy derived from ATP hydrolysis to destabilize and unwind RNA duplexes. The most well-characterized and ubiquitous family of RNA helicases is the DEAD-box family, so named for the conserved B-type ATP-binding motif which is diagnostic of proteins in this family. Over 40 DEAD-box helicases have been identified in organisms as diverse as bacteria, insects, yeast, amphibians, mammals, and plants. DEAD-box helicases function in diverse processes such as translation initiation, splicing, ribosome assembly, and RNA editing, transport, and stability. Some DEAD-box helicases play tissue- and stage-specific roles in spermatogenesis and embryogenesis. Overexpression of the DEAD-box 1 protein (DDX1) may play a role in the progression of neuroblastoma (Nb) and retinoblastoma (Rb) tumors (Godbout, R. et al. (1998) J. Biol. Chem. 273:21161-21168). These observations suggest that DDX1 may promote or enhance tumor progression by altering the normal secondary structure and expression levels of RNA in cancer cells. Other DEAD-box helicases have been implicated either directly or indirectly in tumorigenesis (Discussed in Godbout, supra). For example, murine p68 is mutated in ultraviolet light-induced tumors, and human DDX6 is located at a chromosomal breakpoint associated with B-cell lymphoma. Similarly, a chimeric protein comprised of DDX10 and NUP98, a nucleoporin protein, may be involved in the pathogenesis of certain myeloid malignancies.

Topoisomerases

Besides the need to separate DNA strands prior to replication, the two strands must be "unwound" from one another prior to their separation by DNA helicases. This function is performed by proteins known as DNA topoisomerases. DNA topoisomerase effectively acts as a reversible nuclease that hydrolyzes a phosphodiesterase bond in a DNA strand, permitting the two strands to rotate freely about one another to remove the strain of the helix, and then rejoins the original phosphodiester bond between the two strands. Two types of DNA topoisomerase exist, types I and II. DNA Topoisomerase I causes a single-strand break in a DNA helix to allow the rotation of the two strands of the helix about the remaining phosphodiester bond in the opposite strand. DNA topoisomerase II causes a transient break in both strands of a DNA helix where two double helices cross over one another. This type of topoisomerase can efficiently separate two interlocked DNA

circles (Alberts, supra, pp.260-262). Type II topoisomerases are largely confined to proliferating cells in eukaryotes, such as cancer cells. For this reason they are targets for anticancer drugs. Topoisomerase II has been implicated in multi-drug resistance (MDR) as it appears to aid in the repair of DNA damage inflicted by DNA binding agents such as doxorubicin and vincristine.

Recombinases

Genetic recombination is the process of rearranging DNA sequences within an organism's genome to provide genetic variation for the organism in response to changes in the environment. DNA recombination allows variation in the particular combination of genes present in an individual's genome, as well as the timing and level of expression of these genes (see Alberts, supra, pp. 263-273). Two broad classes of genetic recombination are commonly recognized, general recombination and site-specific recombination. General recombination involves genetic exchange between any homologous pair of DNA sequences usually located on two copies of the same chromosome. The process is aided by enzymes called recombinases that "nick" one strand of a DNA duplex more or less randomly and permit exchange with the complementary strand of another duplex. The process does not normally change the arrangement of genes on a chromosome. In site-specific recombination, the recombinase recognizes specific nucleotide sequences present in one or both of the recombining molecules. Base-pairing is not involved in this form of recombination and therefore does not require DNA homology between the recombining molecules. Unlike general recombination, this form of recombination can alter the relative positions of nucleotide sequences in chromosomes.

Splicing Factors

Various proteins are necessary for processing of transcribed RNAs in the nucleus. Pre-mRNA processing steps include capping at the 5' end with methylguanosine, polyadenylating the 3' end, and splicing to remove introns. The primary RNA transcript from DNA is a faithful copy of the gene containing both exon and intron sequences, and the latter sequences must be cut out of the RNA transcript to produce an mRNA that codes for a protein. This "splicing" of the mRNA sequence takes place in the nucleus with the aid of a large, multicomponent ribonucleoprotein complex known as a spliceosome. The spliceosomal complex is composed of five small nuclear ribonucleoprotein particles (snRNPs) designated U1, U2, U4, U5, and U6, and a number of additional proteins. Each snRNP contains a single species of snRNA and about ten proteins. The RNA components of some snRNPs recognize and base pair with intron consensus sequences. The protein components mediate spliceosome assembly and the splicing reaction. Autoantibodies to snRNP proteins are found in the blood of patients with systemic lupus erythematosus (Stryer, L. (1995) Biochemistry, W.H. Freeman and Company, New York NY, p. 863).

Adhesion Molecules

The surface of a cell is rich in transmembrane proteoglycans, glycoproteins, glycolipids, and receptors. These macromolecules mediate adhesion with other cells and with components of the extracellular matrix (ECM). The interaction of the cell with its surroundings profoundly influences cell shape, strength, flexibility, motility, and adhesion. These dynamic properties are intimately associated with signal transduction pathways controlling cell proliferation and differentiation, tissue construction, and embryonic development.

Cadherins

Cadherins comprise a family of calcium-dependent glycoproteins that function in mediating cell-cell adhesion in virtually all solid tissues of multicellular organisms. These proteins share multiple repeats of a cadherin-specific motif, and the repeats form the folding units of the cadherin extracellular domain. Cadherin molecules cooperate to form focal contacts, or adhesion plaques, between adjacent epithelial cells. The cadherin family includes the classical cadherins and protocadherins. Classical cadherins include the E-cadherin, N-cadherin, and P-cadherin subfamilies. E-cadherin is present on many types of epithelial cells and is especially important for embryonic development. N-cadherin is present on nerve, muscle, and lens cells and is also critical for embryonic development. P-cadherin is present on cells of the placenta and epidermis. Recent studies report that protocadherins are involved in a variety of cell-cell interactions (Suzuki, S.T. (1996) J. Cell Sci. 109:2609-2611). The intracellular anchorage of cadherins is regulated by their dynamic association with catenins, a family of cytoplasmic signal transduction proteins associated with the actin cytoskeleton. The anchorage of cadherins to the actin cytoskeleton appears to be regulated by protein tyrosine phosphorylation, and the cadherins are the target of phosphorylation-induced junctional disassembly (Aberle, H. et al. (1996) J. Cell. Biochem. 61:514-523).

Integrins

Integrins are ubiquitous transmembrane adhesion molecules that link the ECM to the internal cytoskeleton. Integrins are composed of two noncovalently associated transmembrane glycoprotein subunits called α and β. Integrins function as receptors that play a role in signal transduction. For example, binding of integrin to its extracellular ligand may stimulate changes in intracellular calcium levels or protein kinase activity (Sjaastad, M.D. and W.J. Nelson (1997) BioEssays 19:47-55). At least ten cell surface receptors of the integrin family recognize the ECM component fibronectin, which is involved in many different biological processes including cell migration and embryogenesis (Johansson, S. et al. (1997) Front. Biosci. 2:D126-D146).

Lectins

Lectins comprise a ubiquitous family of extracellular glycoproteins which bind cell surface carbohydrates specifically and reversibly, resulting in the agglutination of cells (reviewed in Drickamer, K. and M.E. Taylor (1993) Annu. Rev. Cell Biol. 9:237-264). This function is

particularly important for activation of the immune response. Lectins mediate the agglutination and mitogenic stimulation of lymphocytes at sites of inflammation (Lasky, L.A. (1991) J. Cell. Biochem. 45:139-146; Paietta, E. et al. (1989) J. Immunol. 143:2850-2857).

Lectins are further classified into subfamilies based on carbohydrate-binding specificity and other criteria. The galectin subfamily, in particular, includes lectins that bind β-galactoside carbohydrate moieties in a thiol-dependent manner (reviewed in Hadari, Y.R. et al. (1998) J. Biol. Chem. 270:3447-3453). Galectins are widely expressed and developmentally regulated. Because all galectins lack an N-terminal signal peptide, it is suggested that galectins are externalized through an atypical secretory mechanism. Two classes of galectins have been defined based on molecular weight and oligomerization properties. Small galectins form homodimers and are about 14 to 16 kilodaltons in mass, while large galectins are monomeric and about 29-37 kilodaltons.

Galectins contain a characteristic carbohydrate recognition domain (CRD). The CRD is about 140 amino acids and contains several stretches of about 1 - 10 amino acids which are highly conserved among all galectins. A particular 6-amino acid motif within the CRD contains conserved tryptophan and arginine residues which are critical for carbohydrate binding. The CRD of some galectins also contains cysteine residues which may be important for disulfide bond formation. Secondary structure predictions indicate that the CRD forms several β-sheets.

Galectins play a number of roles in diseases and conditions associated with cell-cell and cell-matrix interactions. For example, certain galectins associate with sites of inflammation and bind to cell surface immunoglobulin E molecules. In addition, galectins may play an important role in cancer metastasis. Galectin overexpression is correlated with the metastatic potential of cancers in humans and mice. Moreover, anti-galectin antibodies inhibit processes associated with cell transformation, such as cell aggregation and anchorage-independent growth (See, for example, Su, Z.-Z. et al. (1996) Proc. Natl. Acad. Sci. USA 93:7252-7257).

Selectins

Selectins, or LEC-CAMs, comprise a specialized lectin subfamily involved primarily in inflammation and leukocyte adhesion (Reviewed in Lasky, supra). Selectins mediate the recruitment of leukocytes from the circulation to sites of acute inflammation and are expressed on the surface of vascular endothelial cells in response to cytokine signaling. Selectins bind to specific ligands on the leukocyte cell membrane and enable the leukocyte to adhere to and migrate along the endothelial surface. Binding of selectin to its ligand leads to polarized rearrangement of the actin cytoskeleton and stimulates signal transduction within the leukocyte (Brenner, B. et al. (1997) Biochem. Biophys. Res. Commun. 231:802-807; Hidari, K.I. et al. (1997) J. Biol. Chem. 272:28750-28756). Members of the selectin family possess three characteristic motifs: a lectin or carbohydrate recognition domain; an epidermal growth factor-like domain; and a variable number of short consensus repeats (scr or

"sushi" repeats) which are also present in complement regulatory proteins. The selectins include lymphocyte adhesion molecule-1 (Lam-1 or L-selectin), endothelial leukocyte adhesion molecule-1 (ELAM-1 or E-selectin), and granule membrane protein-140 (GMP-140 or P-selectin) (Johnston, G.I. et al. (1989) Cell 56:1033-1044).

Antigen Recognition Molecules

SEQ ID NO:37 encodes, for example, an antigen recognition molecule.

All vertebrates have developed sophisticated and complex immune systems that provide protection from viral, bacterial, fungal, and parasitic infections. A key feature of the immune system is its ability to distinguish foreign molecules, or antigens, from "self" molecules. This ability is mediated primarily by secreted and transmembrane proteins expressed by leukocytes (white blood cells) such as lymphocytes, granulocytes, and monocytes. Most of these proteins belong to the immunoglobulin (Ig) superfamily, members of which contain one or more repeats of a conserved structural domain. This Ig domain is comprised of antiparallel β sheets joined by a disulfide bond in an arrangement called the Ig fold. Members of the Ig superfamily include T-cell receptors, major histocompatibility (MHC) proteins, antibodies, and immune cell-specific surface markers such as CD4, CD8, and CD28.

MHC proteins are cell surface markers that bind to and present foreign antigens to T cells. MHC molecules are classified as either class I or class II. Class I MHC molecules (MHC I) are expressed on the surface of almost all cells and are involved in the presentation of antigen to cytotoxic T cells. For example, a cell infected with virus will degrade intracellular viral proteins and express the protein fragments bound to MHC I molecules on the cell surface. The MHC I/antigen complex is recognized by cytotoxic T-cells which destroy the infected cell and the virus within. Class II MHC molecules are expressed primarily on specialized antigen-presenting cells of the immune system, such as B-cells and macrophages. These cells ingest foreign proteins from the extracellular fluid and express MHC II/antigen complex on the cell surface. This complex activates helper T-cells, which then secrete cytokines and other factors that stimulate the immune response. MHC molecules also play an important role in organ rejection following transplantation. Rejection occurs when the recipient's T-cells respond to foreign MHC molecules on the transplanted organ in the same way as to self MHC molecules bound to foreign antigen. (Reviewed in Alberts, B. et al. (1994) Molecular Biology of the Cell, Garland Publishing, New York NY, pp. 1229-1246.)

Antibodies, or immunoglobulins, are either expressed on the surface of B-cells or secreted by B-cells into the circulation. Antibodies bind and neutralize foreign antigens in the blood and other extracellular fluids. The prototypical antibody is a tetramer consisting of two identical heavy polypeptide chains (H-chains) and two identical light polypeptide chains (L-chains) interlinked by

disulfide bonds. This arrangement confers the characteristic Y-shape to antibody molecules. Antibodies are classified based on their H-chain composition. The five antibody classes, IgA, IgD, IgE, IgG and IgM, are defined by the α, δ, ϵ, γ, and μ H-chain types. There are two types of L-chains, κ and λ, either of which may associate as a pair with any H-chain pair. IgG, the most common class of antibody found in the circulation, is tetrameric, while the other classes of antibodies are generally variants or multimers of this basic structure.

H-chains and L-chains each contain an N-terminal variable region and a C-terminal constant region. The constant region consists of about 110 amino acids in L-chains and about 330 or 440 amino acids in H-chains. The amino acid sequence of the constant region is nearly identical among H- or L-chains of a particular class. The variable region consists of about 110 amino acids in both H- and L-chains. However, the amino acid sequence of the variable region differs among H- or L-chains of a particular class. Within each H- or L-chain variable region are three hypervariable regions of extensive sequence diversity, each consisting of about 5 to 10 amino acids. In the antibody molecule, the H- and L-chain hypervariable regions come together to form the antigen recognition site. (Reviewed in Alberts, supra, pp. 1206-1213 and 1216-1217.)

Both H-chains and L-chains contain repeated Ig domains. For example, a typical H-chain contains four Ig domains, three of which occur within the constant region and one of which occurs within the variable region and contributes to the formation of the antigen recognition site. Likewise, a typical L-chain contains two Ig domains, one of which occurs within the constant region and one of which occurs within the variable region.

The immune system is capable of recognizing and responding to any foreign molecule that enters the body. Therefore, the immune system must be armed with a full repertoire of antibodies against all potential antigens. Such antibody diversity is generated by somatic rearrangement of gene segments encoding variable and constant regions. These gene segments are joined together by site-specific recombination which occurs between highly conserved DNA sequences that flank each gene segment. Because there are hundreds of different gene segments, millions of unique genes can be generated combinatorially. In addition, imprecise joining of these segments and an unusually high rate of somatic mutation within these segments further contribute to the generation of a diverse antibody population.

T-cell receptors are both structurally and functionally related to antibodies. (Reviewed in Alberts, supra, pp. 1228-1229.) T-cell receptors are cell surface proteins that bind foreign antigens and mediate diverse aspects of the immune response. A typical T-cell receptor is a heterodimer comprised of two disulfide-linked polypeptide chains called α and β. Each chain is about 280 amino acids in length and contains one variable region and one constant region. Each variable or constant region folds into an Ig domain. The variable regions from the α and β chains come together in the heterodimer to

form the antigen recognition site. T-cell receptor diversity is generated by somatic rearrangement of gene segments encoding the α and β chains. T-cell receptors recognize small peptide antigens that are expressed on the surface of antigen-presenting cells and pathogen-infected cells. These peptide antigens are presented on the cell surface in association with major histocompatibility proteins which provide the proper context for antigen recognition.

Secreted and Extracellular Matrix Molecules

SEQ ID NO:38 and SEQ ID NO:39 encode, for example, secreted/extracellular matrix molecules.

Protein secretion is essential for cellular function. Protein secretion is mediated by a signal peptide located at the amino terminus of the protein to be secreted. The signal peptide is comprised of about ten to twenty hydrophobic amino acids which target the nascent protein from the ribosome to the endoplasmic reticulum (ER). Proteins targeted to the ER may either proceed through the secretory pathway or remain in any of the secretory organelles such as the ER, Golgi apparatus, or lysosomes. Proteins that transit through the secretory pathway are either secreted into the extracellular space or retained in the plasma membrane. Secreted proteins are often synthesized as inactive precursors that are activated by post-translational processing events during transit through the secretory pathway. Such events include glycosylation, proteolysis, and removal of the signal peptide by a signal peptidase. Other events that may occur during protein transport include chaperone-dependent unfolding and folding of the nascent protein and interaction of the protein with a receptor or pore complex. Examples of secreted proteins with amino terminal signal peptides include receptors, extracellular matrix molecules, cytokines, hormones, growth and differentiation factors, neuropeptides, vasomediators, ion channels, transporters/pumps, and proteases. (Reviewed in Alberts, B. et al. (1994) Molecular Biology of The Cell, Garland Publishing, New York NY, pp. 557-560, 582-592.)

The extracellular matrix (ECM) is a complex network of glycoproteins, polysaccharides, proteoglycans, and other macromolecules that are secreted from the cell into the extracellular space. The ECM remains in close association with the cell surface and provides a supportive meshwork that profoundly influences cell shape, motility, strength, flexibility, and adhesion. In fact, adhesion of a cell to its surrounding matrix is required for cell survival except in the case of metastatic tumor cells, which have overcome the need for cell-ECM anchorage. This phenomenon suggests that the ECM plays a critical role in the molecular mechanisms of growth control and metastasis. (Reviewed in Ruoslahti, E. (1996) Sci. Am. 275:72-77.) Furthermore, the ECM determines the structure and physical properties of connective tissue and is particularly important for morphogenesis and other processes associated with embryonic development and pattern formation.

The collagens comprise a family of ECM proteins that provide structure to bone, teeth, skin, ligaments, tendons, cartilage, blood vessels, and basement membranes. Multiple collagen proteins have been identified. Three collagen molecules fold together in a triple helix stabilized by interchain disulfide bonds. Bundles of these triple helices then associate to form fibrils. Collagen primary structure consists of hundreds of (Gly-X-Y) repeats where about a third of the X and Y residues are Pro. Glycines are crucial to helix formation as the bulkier amino acid sidechains cannot fold into the triple helical conformation. Because of these strict sequence requirements, mutations in collagen genes have severe consequences. Osteogenesis imperfecta patients have brittle bones that fracture easily; in severe cases patients die in utero or at birth. Ehlers-Danlos syndrome patients have hyperelastic skin, hypermobile joints, and susceptibility to aortic and intestinal rupture. Chondrodysplasia patients have short stature and ocular disorders. Alport syndrome patients have hematuria, sensorineural deafness, and eye lens deformation. (Isselbacher, K.J. et al. (1994) Harrison's Principles of Internal Medicine, McGraw-Hill, Inc., New York NY, pp. 2105-2117; and Creighton, T.E. (1984) Proteins, Structures and Molecular Principles, W.H. Freeman and Company, New York NY, pp. 191-197.)

Elastin and related proteins confer elasticity to tissues such as skin, blood vessels, and lungs. Elastin is a highly hydrophobic protein of about 750 amino acids that is rich in proline and glycine residues. Elastin molecules are highly cross-linked, forming an extensive extracellular network of fibers and sheets. Elastin fibers are surrounded by a sheath of microfibrils which are composed of a number of glycoproteins, including fibrillin. Mutations in the gene encoding fibrillin are responsible for Marfan's syndrome, a genetic disorder characterized by defects in connective tissue. In severe cases, the aortas of afflicted individuals are prone to rupture. (Reviewed in Alberts, supra, pp. 984-986.)

Fibronectin is a large ECM glycoprotein found in all vertebrates. Fibronectin exists as a dimer of two subunits, each containing about 2,500 amino acids. Each subunit folds into a rod-like structure containing multiple domains. The domains each contain multiple repeated modules, the most common of which is the type III fibronectin repeat. The type III fibronectin repeat is about 90 amino acids in length and is also found in other ECM proteins and in some plasma membrane and cytoplasmic proteins. Furthermore, some type III fibronectin repeats contain a characteristic tripeptide consisting of Arginine-Glycine-Aspartic acid (RGD). The RGD sequence is recognized by the integrin family of cell surface receptors and is also found in other ECM proteins. Disruption of both copies of the gene encoding fibronectin causes early embryonic lethality in mice. The mutant embryos display extensive morphological defects, including defects in the formation of the notochord, somites, heart, blood vessels, neural tube, and extraembryonic structures. (Reviewed in Alberts, supra, pp. 986-987.)

Laminin is a major glycoprotein component of the basal lamina which underlies and supports epithelial cell sheets. Laminin is one of the first ECM proteins synthesized in the developing embryo.

Laminin is an 850 kilodalton protein composed of three polypeptide chains joined in the shape of a cross by disulfide bonds. Laminin is especially important for angiogenesis and in particular, for guiding the formation of capillaries. (Reviewed in Alberts, supra, pp. 990-991.)

There are many other types of proteinaceous ECM components, most of which can be classified as proteoglycans. Proteoglycans are composed of unbranched polysaccharide chains (glycosaminoglycans) attached to protein cores. Common proteoglycans include aggrecan, betaglycan, decorin, perlecan, serglycin, and syndecan-1. Some of these molecules not only provide mechanical support, but also bind to extracellular signaling molecules, such as fibroblast growth factor and transforming growth factor β, suggesting a role for proteoglycans in cell-cell communication and cell growth. (Reviewed in Alberts, supra, pp. 973-978.) Likewise, the glycoproteins tenascin-C and tenascin-R are expressed in developing and lesioned neural tissue and provide stimulatory and anti-adhesive (inhibitory) properties, respectively, for axonal growth. (Faissner, A. (1997) Cell Tissue Res. 290:331-341.)

Cytoskeletal Molecules

SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, and SEQ ID NO:45 encode, for example, cytoskeletal molecules.

The cytoskeleton is a cytoplasmic network of protein fibers that mediate cell shape, structure, and movement. The cytoskeleton supports the cell membrane and forms tracks along which organelles and other elements move in the cytosol. The cytoskeleton is a dynamic structure that allows cells to adopt various shapes and to carry out directed movements. Major cytoskeletal fibers include the microtubules, the microfilaments, and the intermediate filaments. Motor proteins, including myosin, dynein, and kinesin, drive movement of or along the fibers. The motor protein dynamin drives the formation of membrane vesicles. Accessory or associated proteins modify the structure or activity of the fibers while cytoskeletal membrane anchors connect the fibers to the cell membrane.

Tubulins

Microtubules, cytoskeletal fibers with a diameter of about 24 nm, have multiple roles in the cell. Bundles of microtubules form cilia and flagella, which are whip-like extensions of the cell membrane that are necessary for sweeping materials across an epithelium and for swimming of sperm, respectively. Marginal bands of microtubules in red blood cells and platelets are important for these cells' pliability. Organelles, membrane vesicles, and proteins are transported in the cell along tracks of microtubules. For example, microtubules run through nerve cell axons, allowing bi-directional transport of materials and membrane vesicles between the cell body and the nerve

terminal. Failure to supply the nerve terminal with these vesicles blocks the transmission of neural signals. Microtubules are also critical to chromosomal movement during cell division. Both stable and short-lived populations of microtubules exist in the cell.

Microtubules are polymers of GTP-binding tubulin protein subunits. Each subunit is a heterodimer of α- and β- tubulin, multiple isoforms of which exist. The hydrolysis of GTP is linked to the addition of tubulin subunits at the end of a microtubule. The subunits interact head to tail to form protofilaments; the protofilaments interact side to side to form a microtubule. A microtubule is polarized, one end ringed with α-tubulin and the other with β-tubulin, and the two ends differ in their rates of assembly. Generally, each microtubule is composed of 13 protofilaments although 11 or 15 protofilament-microtubules are sometimes found. Cilia and flagella contain doublet microtubules. Microtubules grow from specialized structures known as centrosomes or microtubule-organizing centers (MTOCs). MTOCs may contain one or two centrioles, which are pinwheel arrays of triplet microtubules. The basal body, the organizing center located at the base of a cilium or flagellum, contains one centriole. Gamma tubulin present in the MTOC is important for nucleating the polymerization of α- and β- tubulin heterodimers but does not polymerize into microtubules.

Microtubule-Associated Proteins

Microtubule-associated proteins (MAPs) have roles in the assembly and stabilization of microtubules. One major family of MAPs, assembly MAPs, can be identified in neurons as well as non-neuronal cells. Assembly MAPs are responsible for cross-linking microtubules in the cytosol. These MAPs are organized into two domains: a basic microtubule-binding domain and an acidic projection domain. The projection domain is the binding site for membranes, intermediate filaments, or other microtubules. Based on sequence analysis, assembly MAPs can be further grouped into two types: Type I and Type II. Type I MAPs, which include MAP1A and MAP1B, are large, filamentous molecules that co-purify with microtubules and are abundantly expressed in brain and testes. Type I MAPs contain several repeats of a positively-charged amino acid sequence motif that binds and neutralizes negatively charged tubulin, leading to stabilization of microtubules. MAP1A and MAP1B are each derived from a single precursor polypeptide that is subsequently proteolytically processed to generate one heavy chain and one light chain.

Another light chain, LC3, is a 16.4 kDa molecule that binds MAP1A, MAP1B, and microtubules. It is suggested that LC3 is synthesized from a source other than the MAP1A or MAP1B transcripts, and that the expression of LC3 may be important in regulating the microtubule binding activity of MAP1A and MAP1B during cell proliferation (Mann, S.S. et al. (1994) J. Biol. Chem. 269:11492-11497).

Type II MAPs, which include MAP2a, MAP2b, MAP2c, MAP4, and Tau, are characterized

by three to four copies of an 18-residue sequence in the microtubule-binding domain. MAP2a, MAP2b, and MAP2c are found only in dendrites, MAP4 is found in non-neuronal cells, and Tau is found in axons and dendrites of nerve cells. Alternative splicing of the Tau mRNA leads to the existence of multiple forms of Tau protein. Tau phosphorylation is altered in neurodegenerative disorders such as Alzheimer's disease, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, and familial frontotemporal dementia and Parkinsonism linked to chromosome 17. The altered Tau phosphorylation leads to a collapse of the microtubule network and the formation of intraneuronal Tau aggregates (Spillantini, M.G. and M. Goedert (1998) Trends Neurosci. 21:428-433).

The protein pericentrin is found in the MTOC and has a role in microtubule assembly.

Actins

Microfilaments, cytoskeletal filaments with a diameter of about 7-9 nm, are vital to cell locomotion, cell shape, cell adhesion, cell division, and muscle contraction. Assembly and disassembly of the microfilaments allow cells to change their morphology. Microfilaments are the polymerized form of actin, the most abundant intracellular protein in the eukaryotic cell. Human cells contain six isoforms of actin. The three α-actins are found in different kinds of muscle, nonmuscle β-actin and nonmuscle γ-actin are found in nonmuscle cells, and another γ-actin is found in intestinal smooth muscle cells. G-actin, the monomeric form of actin, polymerizes into polarized, helical F-actin filaments, accompanied by the hydrolysis of ATP to ADP. Actin filaments associate to form bundles and networks, providing a framework to support the plasma membrane and determine cell shape. These bundles and networks are connected to the cell membrane. In muscle cells, thin filaments containing actin slide past thick filaments containing the motor protein myosin during contraction. A family of actin-related proteins exist that are not part of the actin cytoskeleton, but rather associate with microtubules and dynein.

Actin-Associated Proteins

Actin-associated proteins have roles in cross-linking, severing, and stabilization of actin filaments and in sequestering actin monomers. Several of the actin-associated proteins have multiple functions. Bundles and networks of actin filaments are held together by actin cross-linking proteins. These proteins have two actin-binding sites, one for each filament. Short cross-linking proteins promote bundle formation while longer, more flexible cross-linking proteins promote network formation. Calmodulin-like calcium-binding domains in actin cross-linking proteins allow calcium regulation of cross-linking. Group I cross-linking proteins have unique actin-binding domains and include the 30 kD protein, EF-1a, fascin, and scruin. Group II cross-linking proteins have a 7,000-MW actin-binding domain and include villin and dematin. Group III cross-linking proteins have pairs of a 26,000-MW actin-binding domain and include fimbrin, spectrin, dystrophin, ABP 120, and filamin.

Severing proteins regulate the length of actin filaments by breaking them into short pieces or by blocking their ends. Severing proteins include gCAP39, severin (fragmin), gelsolin, and villin. Capping proteins can cap the ends of actin filaments, but cannot break filaments. Capping proteins include CapZ and tropomodulin. The proteins thymosin and profilin sequester actin monomers in the cytosol, allowing a pool of unpolymerized actin to exist. The actin-associated proteins tropomyosin, troponin, and caldesmon regulate muscle contraction in response to calcium.

Intermediate Filaments and Associated Proteins

Intermediate filaments (IFs) are cytoskeletal fibers with a diameter of about 10 nm, intermediate between that of microfilaments and microtubules. IFs serve structural roles in the cell, reinforcing cells and organizing cells into tissues. IFs are particularly abundant in epidermal cells and in neurons. IFs are extremely stable, and, in contrast to microfilaments and microtubules, do not function in cell motility.

Five types of IF proteins are known in mammals. Type I and Type II proteins are the acidic and basic keratins, respectively. Heterodimers of the acidic and basic keratins are the building blocks of keratin IFs. Keratins are abundant in soft epithelia such as skin and cornea, hard epithelia such as nails and hair, and in epithelia that line internal body cavities. Mutations in keratin genes lead to epithelial diseases including epidermolysis bullosa simplex, bullous congenital ichthyosiform erythroderma (epidermolytic hyperkeratosis), non-epidermolytic and epidermolytic palmoplantar keratoderma, ichthyosis bullosa of Siemens, pachyonychia congenita, and white sponge nevus. Some of these diseases result in severe skin blistering. (See, e.g., Wawersik, M. et al. (1997) J. Biol. Chem. 272:32557-32565; and Corden L.D. and W.H. McLean (1996) Exp. Dermatol. 5:297-307.)

Type III IF proteins include desmin, glial fibrillary acidic protein, vimentin, and peripherin. Desmin filaments in muscle cells link myofibrils into bundles and stabilize sarcomeres in contracting muscle. Glial fibrillary acidic protein filaments are found in the glial cells that surround neurons and astrocytes. Vimentin filaments are found in blood vessel endothelial cells, some epithelial cells, and mesenchymal cells such as fibroblasts, and are commonly associated with microtubules. Vimentin filaments may have roles in keeping the nucleus and other organelles in place in the cell. Type IV IFs include the neurofilaments and nestin. Neurofilaments, composed of three polypeptides NF-L, NF-M, and NF-H, are frequently associated with microtubules in axons. Neurofilaments are responsible for the radial growth and diameter of an axon, and ultimately for the speed of nerve impulse transmission. Changes in phosphorylation and metabolism of neurofilaments are observed in neurodegenerative diseases including amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease (Julien, J.P. and W.E. Mushynski (1998) Prog. Nucleic Acid Res. Mol. Biol. 61:1-23). Type V IFs, the lamins, are found in the nucleus where they support the nuclear membrane.

IFs have a central α-helical rod region interrupted by short nonhelical linker segments. The rod region is bracketed, in most cases, by non-helical head and tail domains. The rod regions of intermediate filament proteins associate to form a coiled-coil dimer. A highly ordered assembly process leads from the dimers to the IFs. Neither ATP nor GTP is needed for IF assembly, unlike that of microfilaments and microtubules.

IF-associated proteins (IFAPs) mediate the interactions of IFs with one another and with other cell structures. IFAPs cross-link IFs into a bundle, into a network, or to the plasma membrane, and may cross-link IFs to the microfilament and microtubule cytoskeleton. Microtubules and IFs are in particular closely associated. IFAPs include BPAG1, plakoglobin, desmoplakin I, desmoplakin II, plectin, ankyrin, filaggrin, and lamin B receptor.

Cytoskeletal-Membrane Anchors

Cytoskeletal fibers are attached to the plasma membrane by specific proteins. These attachments are important for maintaining cell shape and for muscle contraction. In erythrocytes, the spectrin-actin cytoskeleton is attached to cell membrane by three proteins, band 4.1, ankyrin, and adducin. Defects in this attachment result in abnormally shaped cells which are more rapidly degraded by the spleen, leading to anemia. In platelets, the spectrin-actin cytoskeleton is also linked to the membrane by ankyrin; a second actin network is anchored to the membrane by filamin. In muscle cells the protein dystrophin links actin filaments to the plasma membrane; mutations in the dystrophin gene lead to Duchenne muscular dystrophy. In adherens junctions and adhesion plaques the peripheral membrane proteins α-actinin and vinculin attach actin filaments to the cell membrane.

IFs are also attached to membranes by cytoskeletal-membrane anchors. The nuclear lamina is attached to the inner surface of the nuclear membrane by the lamin B receptor. Vimentin IFs are attached to the plasma membrane by ankyrin and plectin. Desmosome and hemidesmosome membrane junctions hold together epithelial cells of organs and skin. These membrane junctions allow shear forces to be distributed across the entire epithelial cell layer, thus providing strength and rigidity to the epithelium. IFs in epithelial cells are attached to the desmosome by plakoglobin and desmoplakins. The proteins that link IFs to hemidesmosomes are not known. Desmin IFs surround the sarcomere in muscle and are linked to the plasma membrane by paranemin, synemin, and ankyrin.

Myosin-related Motor Proteins

Myosins are actin-activated ATPases, found in eukaryotic cells, that couple hydrolysis of ATP with motion. Myosin provides the motor function for muscle contraction and intracellular movements such as phagocytosis and rearrangement of cell contents during mitotic cell division (cytokinesis). The contractile unit of skeletal muscle, termed the sarcomere, consists of highly ordered arrays of thin actin-containing filaments and thick myosin-containing filaments. Crossbridges form

between the thick and thin filaments, and the ATP-dependent movement of myosin heads within the thick filaments pulls the thin filaments, shortening the sarcomere and thus the muscle fiber.

Myosins are composed of one or two heavy chains and associated light chains. Myosin heavy chains contain an amino-terminal motor or head domain, a neck that is the site of light-chain binding, and a carboxy-terminal tail domain. The tail domains may associate to form an α-helical coiled coil. Conventional myosins, such as those found in muscle tissue, are composed of two myosin heavy-chain subunits, each associated with two light-chain subunits that bind at the neck region and play a regulatory role. Unconventional myosins, believed to function in intracellular motion, may contain either one or two heavy chains and associated light chains. There is evidence for about 25 myosin heavy chain genes in vertebrates, more than half of them unconventional.

<u>Dynein-related Motor Proteins</u>

Dyneins are (-) end-directed motor proteins which act on microtubules. Two classes of dyneins, cytosolic and axonemal, have been identified. Cytosolic dyneins are responsible for translocation of materials along cytoplasmic microtubules, for example, transport from the nerve terminal to the cell body and transport of endocytic vesicles to lysosomes. Cytoplasmic dyneins are also reported to play a role in mitosis. Axonemal dyneins are responsible for the beating of flagella and cilia. Dynein on one microtubule doublet walks along the adjacent microtubule doublet. This sliding force produces bending forces that cause the flagellum or cilium to beat. Dyneins have a native mass between 1000 and 2000 kDa and contain either two or three force-producing heads driven by the hydrolysis of ATP. The heads are linked via stalks to a basal domain which is composed of a highly variable number of accessory intermediate and light chains.

<u>Kinesin-related Motor Proteins</u>

Kinesins are (+) end-directed motor proteins which act on microtubules. The prototypical kinesin molecule is involved in the transport of membrane-bound vesicles and organelles. This function is particularly important for axonal transport in neurons. Kinesin is also important in all cell types for the transport of vesicles from the Golgi complex to the endoplasmic reticulum. This role is critical for maintaining the identity and functionality of these secretory organelles.

Kinesins define a ubiquitous, conserved family of over 50 proteins that can be classified into at least 8 subfamilies based on primary amino acid sequence, domain structure, velocity of movement, and cellular function. (Reviewed in Moore, J.D. and S.A. Endow (1996) Bioessays 18:207-219; and Hoyt, A.M. (1994) Curr. Opin. Cell Biol. 6:63-68.) The prototypical kinesin molecule is a heterotetramer comprised of two heavy polypeptide chains (KHCs) and two light polypeptide chains (KLCs). The KHC subunits are typically referred to as "kinesin." KHC is about 1000 amino acids in length, and KLC is about 550 amino acids in length. Two KHCs dimerize to form a rod-shaped molecule with

three distinct regions of secondary structure. At one end of the molecule is a globular motor domain that functions in ATP hydrolysis and microtubule binding. Kinesin motor domains are highly conserved and share over 70% identity. Beyond the motor domain is an α-helical coiled-coil region which mediates dimerization. At the other end of the molecule is a fan-shaped tail that associates with molecular cargo. The tail is formed by the interaction of the KHC C-termini with the two KLCs.

Members of the more divergent subfamilies of kinesins are called kinesin-related proteins (KRPs), many of which function during mitosis in eukaryotes (Hoyt, supra). Some KRPs are required for assembly of the mitotic spindle. In vivo and in vitro analyses suggest that these KRPs exert force on microtubules that comprise the mitotic spindle, resulting in the separation of spindle poles. Phosphorylation of KRP is required for this activity. Failure to assemble the mitotic spindle results in abortive mitosis and chromosomal aneuploidy, the latter condition being characteristic of cancer cells. In addition, a unique KRP, centromere protein E, localizes to the kinetochore of human mitotic chromosomes and may play a role in their segregation to opposite spindle poles.

Dynamin-related Motor Proteins

Dynamin is a large GTPase motor protein that functions as a "molecular pinchase," generating a mechanochemical force used to sever membranes. This activity is important in forming clathrin-coated vesicles from coated pits in endocytosis and in the biogenesis of synaptic vesicles in neurons. Binding of dynamin to a membrane leads to dynamin's self-assembly into spirals that may act to constrict a flat membrane surface into a tubule. GTP hydrolysis induces a change in conformation of the dynamin polymer that pinches the membrane tubule, leading to severing of the membrane tubule and formation of a membrane vesicle. Release of GDP and inorganic phosphate leads to dynamin disassembly. Following disassembly the dynamin may either dissociate from the membrane or remain associated to the vesicle and be transported to another region of the cell. Three homologous dynamin genes have been discovered, in addition to several dynamin-related proteins. Conserved dynamin regions are the N-terminal GTP-binding domain, a central pleckstrin homology domain that binds membranes, a central coiled-coil region that may activate dynamin's GTPase activity, and a C-terminal proline-rich domain that contains several motifs that bind SH3 domains on other proteins. Some dynamin-related proteins do not contain the pleckstrin homology domain or the proline-rich domain. (See McNiven, M.A. (1998) Cell 94:151-154; Scaife, R.M. and R.L. Margolis (1997) Cell. Signal. 9:395-401.)

The cytoskeleton is reviewed in Lodish, H. et al. (1995) Molecular Cell Biology, Scientific American Books, New York NY.

Ribosomal Molecules

SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, and SEQ ID NO:53 encode, for example, ribosomal molecules.

Ribosomal RNAs (rRNAs) are assembled, along with ribosomal proteins, into ribosomes, which are cytoplasmic particles that translate messenger RNA into polypeptides. The eukaryotic ribosome is composed of a 60S (large) subunit and a 40S (small) subunit, which together form the 80S ribosome. In addition to the 18S, 28S, 5S, and 5.8S rRNAs, the ribosome also contains more than fifty proteins. The ribosomal proteins have a prefix which denotes the subunit to which they belong, either L (large) or S (small). Ribosomal protein activities include binding rRNA and organizing the conformation of the junctions between rRNA helices (Woodson, S.A. and N.B. Leontis (1998) Curr. Opin. Struct. Biol. 8:294-300; Ramakrishnan, V. and S.W. White (1998) Trends Biochem. Sci. 23:208-212.) Three important sites are identified on the ribosome. The aminoacyl-tRNA site (A site) is where charged tRNAs (with the exception of the initiator-tRNA) bind on arrival at the ribosome. The peptidyl-tRNA site (P site) is where new peptide bonds are formed, as well as where the initiator tRNA binds. The exit site (E site) is where deacylated tRNAs bind prior to their release from the ribosome. (The ribosome is reviewed in Stryer, L. (1995) Biochemistry W.H. Freeman and Company, New York NY, pp. 888-908; and Lodish, H. et al. (1995) Molecular Cell Biology Scientific American Books, New York NY. pp. 119-138.)

Chromatin Molecules

The nuclear DNA of eukaryotes is organized into chromatin. Two types of chromatin are observed: euchromatin, some of which may be transcribed, and heterochromatin so densely packed that much of it is inaccessible to transcription. Chromatin packing thus serves to regulate protein expression in eukaryotes. Bacteria lack chromatin and the chromatin-packing level of gene regulation.

The fundamental unit of chromatin is the nucleosome of 200 DNA base pairs associated with two copies each of histones H2A, H2B, H3, and H4. Adjacent nucleosomes are linked by another class of histones, H1. Low molecular weight non-histone proteins called the high mobility group (HMG), associated with chromatin, may function in the unwinding of DNA and stabilization of single-stranded DNA. Chromodomain proteins function in compaction of chromatin into its transcriptionally silent heterochromatin form.

During mitosis, all DNA is compacted into heterochromatin and transcription ceases. Transcription in interphase begins with the activation of a region of chromatin. Active chromatin is decondensed. Decondensation appears to be accompanied by changes in binding coefficient, phosphorylation and acetylation states of chromatin histones. HMG proteins HMG13 and HMG17 selectively bind activated chromatin. Topoisomerases remove superhelical tension on DNA. The

activated region decondenses, allowing gene regulatory proteins and transcription factors to assemble on the DNA.

Patterns of chromatin structure can be stably inherited, producing heritable patterns of gene expression. In mammals, one of the two X chromosomes in each female cell is inactivated by condensation to heterochromatin during zygote development. The inactive state of this chromosome is inherited, so that adult females are mosaics of clusters of paternal-X and maternal-X clonal cell groups. The condensed X chromosome is reactivated in meiosis.

Chromatin is associated with disorders of protein expression such as thalassemia, a genetic anemia resulting from the removal of the locus control region (LCR) required for decondensation of the globin gene locus.

For a review of chromatin structure and function see Alberts, B. et al. (1994) Molecular Cell Biology, third edition, Garland Publishing, Inc., New York NY, pp. 351-354, 433-439.

Electron Transfer Associated Molecules

Electron carriers such as cytochromes accept electrons from NADH or $FADH_2$ and donate them to other electron carriers. Most electron-transferring proteins, except ubiquinone, are prosthetic groups such as flavins, heme, FeS clusters, and copper, bound to inner membrane proteins. Adrenodoxin, for example, is an FeS protein that forms a complex with NADPH:adrenodoxin reductase and cytochrome p450. Cytochromes contain a heme prosthetic group, a porphyrin ring containing a tightly bound iron atom. Electron transfer reactions play a crucial role in cellular energy production.

Energy is produced by the oxidation of glucose and fatty acids. Glucose is initially converted to pyruvate in the cytoplasm. Fatty acids and pyruvate are transported to the mitochondria for complete oxidation to CO_2 coupled by enzymes to the transport of electrons from NADH and $FADH_2$ to oxygen and to the synthesis of ATP (oxidative phosphorylation) from ADP and P_i.

Pyruvate is transported into the mitochondria and converted to acetyl-CoA for oxidation via the citric acid cycle, involving pyruvate dehydrogenase components, dihydrolipoyl transacetylase, and dihydrolipoyl dehydrogenase. Enzymes involved in the citric acid cycle include: citrate synthetase, aconitases, isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase complex including transsuccinylases, succinyl CoA synthetase, succinate dehydrogenase, fumarases, and malate dehydrogenase. Acetyl CoA is oxidized to CO_2 with concomitant formation of NADH, $FADH_2$, and GTP. In oxidative phosphorylation, the transfer of electrons from NADH and $FADH_2$ to oxygen by dehydrogenases is coupled to the synthesis of ATP from ADP and P_i by the F_0F_1 ATPase complex in the mitochondrial inner membrane. Enzyme complexes responsible for electron transport and ATP

synthesis include the F_0F_1 ATPase complex, ubiquinone(CoQ)-cytochrome c reductase, ubiquinone reductase, cytochrome b, cytochrome c_1, FeS protein, and cytochrome c oxidase.

ATP synthesis requires membrane transport enzymes including the phosphate transporter and the ATP-ADP antiport protein. The ATP-binding casette (ABC) superfamily has also been suggested as belonging to the mitochondrial transport group (Hogue, D.L. et al. (1999) J. Mol. Biol. 285:379-389). Brown fat uncoupling protein dissipates oxidative energy as heat, and may be involved the fever response to infection and trauma (Cannon, B. et al. (1998) Ann. NY Acad. Sci. 856:171-187).

Mitochondria are oval-shaped organelles comprising an outer membrane, a tightly folded inner membrane, an intermembrane space between the outer and inner membranes, and a matrix inside the inner membrane. The outer membrane contains many porin molecules that allow ions and charged molecules to enter the intermembrane space, while the inner membrane contains a variety of transport proteins that transfer only selected molecules. Mitochondria are the primary sites of energy production in cells.

Mitochondria contain a small amount of DNA. Human mitochondrial DNA encodes 13 proteins, 22 tRNAs, and 2 rRNAs. Mitochondrial-DNA encoded proteins include NADH-Q reductase, a cytochrome reductase subunit, cytochrome oxidase subunits, and ATP synthase subunits.

Electron-transfer reactions also occur outside the mitochondria in locations such as the endoplasmic reticulum, which plays a crucial role in lipid and protein biosynthesis. Cytochrome b5 is a central electron donor for various reductive reactions occurring on the cytoplasmic surface of liver endoplasmic reticulum. Cytochrome b5 has been found in Golgi, plasma, endoplasmic reticulum (ER), and microbody membranes.

For a review of mitochondrial metabolism and regulation, see Lodish, H. et al. (1995) Molecular Cell Biology, Scientific American Books, New York NY, pp. 745-797 and Stryer (1995) Biochemistry, W.H. Freeman and Co., San Francisco CA, pp 529-558, 988-989.

The majority of mitochondrial proteins are encoded by nuclear genes, are synthesized on cytosolic ribosomes, and are imported into the mitochondria. Nuclear-encoded proteins which are destined for the mitochondrial matrix typically contain positively-charged amino terminal signal sequences. Import of these preproteins from the cytoplasm requires a multisubunit protein complex in the outer membrane known as the translocase of outer mitochondrial membrane (TOM; previously designated MOM; Pfanner, N. et al. (1996) Trends Biochem. Sci. 21:51-52) and at least three inner membrane proteins which comprise the translocase of inner mitochondrial membrane (TIM; previously designated MIM; Pfanner, supra). An inside-negative membrane potential across the inner mitochondrial membrane is also required for preprotein import. Preproteins are recognized by surface receptor components of the TOM complex and are translocated through a proteinaceous pore formed by other TOM components. Proteins targeted to the matrix are then recognized by the import

machinery of the TIM complex. The import systems of the outer and inner membranes can function independently (Segui-Real, B. et al. (1993) EMBO J. 12:2211-2218).

Once precursor proteins are in the mitochondria, the leader peptide is cleaved by a signal peptidase to generate the mature protein. Most leader peptides are removed in a one step process by a protease termed mitochondrial processing peptidase (MPP) (Paces, V. et al. (1993) Proc. Natl. Acad. Sci. USA 90:5355-5358). In some cases a two-step process occurs in which MPP generates an intermediate precursor form which is cleaved by a second enzyme, mitochondrial intermediate peptidase, to generate the mature protein.

Mitochondrial dysfunction leads to impaired calcium buffering, generation of free radicals that may participate in deleterious intracellular and extracellular processes, changes in mitochondrial permeability and oxidative damage which is observed in several neurodegenerative diseases. Neurodegenerative diseases linked to mitochondrial dysfunction include some forms of Alzheimer's disease, Friedreich's ataxia, familial amyotrophic lateral sclerosis, and Huntington's disease (Beal, M.F. (1998) Biochim. Biophys. Acta 1366:211-213). The myocardium is heavily dependent on oxidative metabolism, so mitochondrial dysfunction often leads to heart disease (DiMauro, S. and M. Hirano (1998) Curr. Opin. Cardiol 13:190-197). Mitochondria are implicated in disorders of cell proliferation, since they play an important role in a cell's decision to proliferate or self-destruct through apoptosis. The oncoprotein Bcl-2, for example, promotes cell proliferation by stabilizing mitochondrial membranes so that apoptosis signals are not released (Susin, S.A. (1998) Biochim. Biophys. Acta 1366:151-165).

Transcription Factor Molecules

SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, and SEQ ID NO:33 encode, for example, transcription factor molecules.

Multicellular organisms are comprised of diverse cell types that differ dramatically both in structure and function. The identity of a cell is determined by its characteristic pattern of gene expression, and different cell types express overlapping but distinctive sets of genes throughout development. Spatial and temporal regulation of gene expression is critical for the control of cell proliferation, cell differentiation, apoptosis, and other processes that contribute to organismal development. Furthermore, gene expression is regulated in response to extracellular signals that mediate cell-cell communication and coordinate the activities of different cell types. Appropriate gene regulation also ensures that cells function efficiently by expressing only those genes whose functions are required at a given time.

Transcriptional regulatory proteins are essential for the control of gene expression. Some of these proteins function as transcription factors that initiate, activate, repress, or terminate gene transcription. Transcription factors generally bind to the promoter, enhancer, and upstream regulatory regions of a gene in a sequence-specific manner, although some factors bind regulatory elements within or downstream of a gene's coding region. Transcription factors may bind to a specific region of DNA singly or as a complex with other accessory factors. (Reviewed in Lewin, B. (1990) Genes IV, Oxford University Press, New York NY, and Cell Press, Cambridge MA, pp. 554-570.)

The double helix structure and repeated sequences of DNA create topological and chemical features which can be recognized by transcription factors. These features are hydrogen bond donor and acceptor groups, hydrophobic patches, major and minor grooves, and regular, repeated stretches of sequence which induce distinct bends in the helix. Typically, transcription factors recognize specific DNA sequence motifs of about 20 nucleotides in length. Multiple, adjacent transcription factor-binding motifs may be required for gene regulation.

Many transcription factors incorporate DNA-binding structural motifs which comprise either α helices or ß sheets that bind to the major groove of DNA. Four well-characterized structural motifs are helix-turn-helix, zinc finger, leucine zipper, and helix-loop-helix. Proteins containing these motifs may act alone as monomers, or they may form homo- or heterodimers that interact with DNA.

The helix-turn-helix motif consists of two α helices connected at a fixed angle by a short chain of amino acids. One of the helices binds to the major groove. Helix-turn-helix motifs are exemplified by the homeobox motif which is present in homeodomain proteins. These proteins are critical for specifying the anterior-posterior body axis during development and are conserved throughout the animal kingdom. The Antennapedia and Ultrabithorax proteins of Drosophila melanogaster are prototypical homeodomain proteins (Pabo, C.O. and R.T. Sauer (1992) Annu. Rev. Biochem. 61:1053-1095).

The zinc finger motif, which binds zinc ions, generally contains tandem repeats of about 30 amino acids consisting of periodically spaced cysteine and histidine residues. Examples of this sequence pattern, designated C2H2 and C3HC4 ("RING" finger), have been described (Lewin, supra). Zinc finger proteins each contain an α helix and an antiparallel ß sheet whose proximity and conformation are maintained by the zinc ion. Contact with DNA is made by the arginine prece ding the α helix and by the second, third, and sixth residues of the α helix. Variants of the zinc finger motif include poorly defined cysteine-rich motifs which bind zinc or other metal ions. These motifs may not contain histidine residues and are generally nonrepetitive.

The leucine zipper motif comprises a stretch of amino acids rich in leucine which can form an amphipathic α helix. This structure provides the basis for dimerization of two leucine zipper

proteins. The region adjacent to the leucine zipper is usually basic, and upon protein dimerization, is optimally positioned for binding to the major groove. Proteins containing such motifs are generally referred to as bZIP transcription factors.

The helix-loop-helix motif (HLH) consists of a short α helix connected by a loop to a longer α helix. The loop is flexible and allows the two helices to fold back against each other and to bind to DNA. The transcription factor Myc contains a prototypical HLH motif.

Most transcription factors contain characteristic DNA binding motifs, and variations on the above motifs and new motifs have been and are currently being characterized (Faisst, S. and S. Meyer (1992) Nucleic Acids Res. 20:3-26).

Many neoplastic disorders in humans can be attributed to inappropriate gene expression. Malignant cell growth may result from either excessive expression of tumor promoting genes or insufficient expression of tumor suppressor genes (Cleary, M.L. (1992) Cancer Surv. 15:89-104). Chromosomal translocations may also produce chimeric loci which fuse the coding sequence of one gene with the regulatory regions of a second unrelated gene. Such an arrangement likely results in inappropriate gene transcription, potentially contributing to malignancy.

In addition, the immune system responds to infection or trauma by activating a cascade of events that coordinate the progressive selection, amplification, and mobilization of cellular defense mechanisms. A complex and balanced program of gene activation and repression is involved in this process. However, hyperactivity of the immune system as a result of improper or insufficient regulation of gene expression may result in considerable tissue or organ damage. This damage is well documented in immunological responses associated with arthritis, allergens, heart attack, stroke, and infections (Isselbacher, K.J. et al. (1996) Harrison's Principles of Internal Medicine, 13/e, McGraw Hill, Inc. and Teton Data Systems Software).

Furthermore, the generation of multicellular organisms is based upon the induction and coordination of cell differentiation at the appropriate stages of development. Central to this process is differential gene expression, which confers the distinct identities of cells and tissues throughout the body. Failure to regulate gene expression during development can result in developmental disorders. Human developmental disorders caused by mutations in zinc finger-type transcriptional regulators include: urogenenital developmental abnormalities associated with WT1; Greig cephalopolysyndactyly, Pallister-Hall syndrome, and postaxial polydactyly type A (GLI3); and Townes-Brocks syndrome, characterized by anal, renal, limb, and ear abnormalities (SALL1) (Engelkamp, D. and V. van Heyningen (1996) Curr. Opin. Genet. Dev. 6:334-342; Kohlhase, J. et al. (1999) Am. J. Hum. Genet. 64:435-445).

Cell Membrane Molecules

SEQ ID NO:46, SEQ ID NO:47, and SEQ ID NO:48 encode, for example, cell membrane molecules.

Eukaryotic cells are surrounded by plasma membranes which enclose the cell and maintain an environment inside the cell that is distinct from its surroundings. In addition, eukaryotic organisms are distinct from prokaryotes in possessing many intracellular organelle and vesicle structures. Many of the metabolic reactions which distinguish eukaryotic biochemistry from prokaryotic biochemistry take place within these structures. The plasma membrane and the membranes surrounding organelles and vesicles are composed of phosphoglycerides, fatty acids, cholesterol, phospholipids, glycolipids, proteoglycans, and proteins. These components confer identity and functionality to the membranes with which they associate.

Integral Membrane Proteins

The majority of known integral membrane proteins are transmembrane proteins (TM) which are characterized by an extracellular, a transmembrane, and an intracellular domain. TM domains are typically comprised of 15 to 25 hydrophobic amino acids which are predicted to adopt an α-helical conformation. TM proteins are classified as bitopic (Types I and II) and polytopic (Types III and IV) (Singer, S.J. (1990) Annu. Rev. Cell Biol. 6:247-296). Bitopic proteins span the membrane once while polytopic proteins contain multiple membrane-spanning segments. TM proteins function as cell-surface receptors, receptor-interacting proteins, transporters of ions or metabolites, ion channels, cell anchoring proteins, and cell type-specific surface antigens.

Many membrane proteins (MPs) contain amino acid sequence motifs that target these proteins to specific subcellular sites. Examples of these motifs include PDZ domains, KDEL, RGD, NGR, and GSL sequence motifs, von Willebrand factor A (vWFA) domains, and EGF-like domains. RGD, NGR, and GSL motif-containing peptides have been used as drug delivery agents in targeted cancer treatment of tumor vasculature (Arap, W. et al. (1998) Science 279:377-380). Furthermore, MPs may also contain amino acid sequence motifs, such as the carbohydrate recognition domain (CRD), that mediate interactions with extracellular or intracellular molecules.

G-Protein Coupled Receptors

G-protein coupled receptors (GPCR) are a superfamily of integral membrane proteins which transduce extracellular signals. GPCRs include receptors for biogenic amines, lipid mediators of inflammation, peptide hormones, and sensory signal mediators. The structure of these highly-conserved receptors consists of seven hydrophobic transmembrane regions, an extracellular N-terminus, and a cytoplasmic C-terminus. Three extracellular loops alternate with three intracellular loops to link the seven transmembrane regions. Cysteine disulfide bridges connect the second and third extracellular loops. The most conserved regions of GPCRs are the transmembrane regions and

the first two cytoplasmic loops. A conserved, acidic-Arg-aromatic residue triplet present in the second cytoplasmic loop may interact with G proteins. A GPCR consensus pattern is characteristic of most proteins belonging to this superfamily (ExPASy PROSITE document PS00237; and Watson, S. and S. Arkinstall (1994) The G-protein Linked Receptor Facts Book, Academic Press, San Diego CA, pp. 2-6). Mutations and changes in transcriptional activation of GPCR-encoding genes have been associated with neurological disorders such as schizophrenia, Parkinson's disease, Alzheimer's disease, drug addiction, and feeding disorders.

Scavenger Receptors

Macrophage scavenger receptors with broad ligand specificity may participate in the binding of low density lipoproteins (LDL) and foreign antigens. Scavenger receptors types I and II are trimeric membrane proteins with each subunit containing a small N-terminal intracellular domain, a transmembrane domain, a large extracellular domain, and a C-terminal cysteine-rich domain. The extracellular domain contains a short spacer region, an α-helical coiled-coil region, and a triple helical collagen-like region. These receptors have been shown to bind a spectrum of ligands, including chemically modified lipoproteins and albumin, polyribonucleotides, polysaccharides, phospholipids, and asbestos (Matsumoto, A. et al. (1990) Proc. Natl. Acad. Sci. USA 87:9133-9137; and Elomaa, O. et al. (1995) Cell 80:603-609). The scavenger receptors are thought to play a key role in atherogenesis by mediating uptake of modified LDL in arterial walls, and in host defense by binding bacterial endotoxins, bacteria, and protozoa.

Tetraspan Family Proteins

The transmembrane 4 superfamily (TM4SF) or tetraspan family is a multigene family encoding type III integral membrane proteins (Wright, M.D. and M.G. Tomlinson (1994) Immunol. Today 15:588-594). The TM4SF is comprised of membrane proteins which traverse the cell membrane four times. Members of the TM4SF include platelet and endothelial cell membrane proteins, melanoma-associated antigens, leukocyte surface glycoproteins, colonal carcinoma antigens, tumor-associated antigens, and surface proteins of the schistosome parasites (Jankowski, S.A. (1994) Oncogene 9:1205-1211). Members of the TM4SF share about 25-30% amino acid sequence identity with one another.

A number of TM4SF members have been implicated in signal transduction, control of cell adhesion, regulation of cell growth and proliferation, including development and oncogenesis, and cell motility, including tumor cell metastasis. Expression of TM4SF proteins is associated with a variety of tumors and the level of expression may be altered when cells are growing or activated.

Tumor Antigens

Tumor antigens are cell surface molecules that are differentially expressed in tumor cells relative to normal cells. Tumor antigens distinguish tumor cells immunologically from normal cells

and provide diagnostic and therapeutic targets for human cancers (Takagi, S. et al. (1995) Int. J. Cancer 61:706-715; Liu, E. et al. (1992) Oncogene 7:1027-1032).

Leukocyte Antigens

Other types of cell surface antigens include those identified on leukocytic cells of the immune system. These antigens have been identified using systematic, monoclonal antibody (mAb)-based "shot gun" techniques. These techniques have resulted in the production of hundreds of mAbs directed against unknown cell surface leukocytic antigens. These antigens have been grouped into "clusters of differentiation" based on common immunocytochemical localization patterns in various differentiated and undifferentiated leukocytic cell types. Antigens in a given cluster are presumed to identify a single cell surface protein and are assigned a "cluster of differentiation" or "CD" designation. Some of the genes encoding proteins identified by CD antigens have been cloned and verified by standard molecular biology techniques. CD antigens have been characterized as both transmembrane proteins and cell surface proteins anchored to the plasma membrane via covalent attachment to fatty acid-containing glycolipids such as glycosylphosphatidylinositol (GPI). (Reviewed in Barclay, A.N. et al. (1995) The Leucocyte Antigen Facts Book, Academic Press, San Diego CA, pp. 17-20.)

Ion Channels

Ion channels are found in the plasma membranes of virtually every cell in the body. For example, chloride channels mediate a variety of cellular functions including regulation of membrane potentials and absorption and secretion of ions across epithelial membranes. Chloride channels also regulate the pH of organelles such as the Golgi apparatus and endosomes (see, e.g., Greger, R. (1988) Annu. Rev. Physiol. 50:111-122). Electrophysiological and pharmacological properties of chloride channels, including ion conductance, current-voltage relationships, and sensitivity to modulators, suggest that different chloride channels exist in muscles, neurons, fibroblasts, epithelial cells, and lymphocytes.

Many ion channels have sites for phosphorylation by one or more protein kinases including protein kinase A, protein kinase C, tyrosine kinase, and casein kinase II, all of which regulate ion channel activity in cells. Inappropriate phosphorylation of proteins in cells has been linked to changes in cell cycle progression and cell differentiation. Changes in the cell cycle have been linked to induction of apoptosis or cancer. Changes in cell differentiation have been linked to diseases and disorders of the reproductive system, immune system, skeletal muscle, and other organ systems.

Proton Pumps

Proton ATPases comprise a large class of membrane proteins that use the energy of ATP hydrolysis to generate an electrochemical proton gradient across a membrane. The resultant gradient may be used to transport other ions across the membrane (Na^+, K^+, or Cl^-) or to maintain organelle

pH. Proton ATPases are further subdivided into the mitochondrial F-ATPases, the plasma membrane ATPases, and the vacuolar ATPases. The vacuolar ATPases establish and maintain an acidic pH within various organelles involved in the processes of endocytosis and exocytosis (Mellman, I. et al. (1986) Annu. Rev. Biochem. 55:663-700).

Proton-coupled, 12 membrane-spanning domain transporters such as PEPT 1 and PEPT 2 are responsible for gastrointestinal absorption and for renal reabsorption of peptides using an electrochemical H^+ gradient as the driving force. Another type of peptide transporter, the TAP transporter, is a heterodimer consisting of TAP 1 and TAP 2 and is associated with antigen processing. Peptide antigens are transported across the membrane of the endoplasmic reticulum by TAP so they can be expressed on the cell surface in association with MHC molecules. Each TAP protein consists of multiple hydrophobic membrane spanning segments and a highly conserved ATP-binding cassette (Boll, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:284-289). Pathogenic microorganisms, such as herpes simplex virus, may encode inhibitors of TAP-mediated peptide transport in order to evade immune surveillance (Marusina, K. and J.J Manaco (1996) Curr. Opin. Hematol. 3:19-26).

ABC Transporters

The ATP-binding cassette (ABC) transporters, also called the "traffic ATPases", comprise a superfamily of membrane proteins that mediate transport and channel functions in prokaryotes and eukaryotes (Higgins, C.F. (1992) Annu. Rev. Cell Biol. 8:67-113). ABC proteins share a similar overall structure and significant sequence homology. All ABC proteins contain a conserved domain of approximately two hundred amino acid residues which includes one or more nucleotide binding domains. Mutations in ABC transporter genes are associated with various disorders, such as hyperbilirubinemia II/Dubin-Johnson syndrome, recessive Stargardt's disease, X-linked adrenoleukodystrophy, multidrug resistance, celiac disease, and cystic fibrosis.

Peripheral and Anchored Membrane Proteins

Some membrane proteins are not membrane-spanning but are attached to the plasma membrane via membrane anchors or interactions with integral membrane proteins. Membrane anchors are covalently joined to a protein post-translationally and include such moieties as prenyl, myristyl, and glycosylphosphatidyl inositol groups. Membrane localization of peripheral and anchored proteins is important for their function in processes such as receptor-mediated signal transduction. For example, prenylation of Ras is required for its localization to the plasma membrane and for its normal and oncogenic functions in signal transduction.

Vesicle Coat Proteins

Intercellular communication is essential for the development and survival of multicellular organisms. Cells communicate with one another through the secretion and uptake of protein

signaling molecules. The uptake of proteins into the cell is achieved by the endocytic pathway, in which the interaction of extracellular signaling molecules with plasma membrane receptors results in the formation of plasma membrane-derived vesicles that enclose and transport the molecules into the cytosol. These transport vesicles fuse with and mature into endosomal and lysosomal (digestive) compartments. The secretion of proteins from the cell is achieved by exocytosis, in which molecules inside of the cell proceed through the secretory pathway. In this pathway, molecules transit from the ER to the Golgi apparatus and finally to the plasma membrane, where they are secreted from the cell.

Several steps in the transit of material along the secretory and endocytic pathways require the formation of transport vesicles. Specifically, vesicles form at the transitional endoplasmic reticulum (tER), the rim of Golgi cisternae, the face of the Trans-Golgi Network (TGN), the plasma membrane (PM), and tubular extensions of the endosomes. Vesicle formation occurs when a region of membrane buds off from the donor organelle. The membrane-bound vesicle contains proteins to be transported and is surrounded by a proteinaceous coat, the components of which are recruited from the cytosol. Two different classes of coat protein have been identified. Clathrin coats form on vesicles derived from the TGN and PM, whereas coatomer (COP) coats form on vesicles derived from the ER and Golgi. COP coats can be further classified as COPI, involved in retrograde traffic through the Golgi and from the Golgi to the ER, and COPII, involved in anterograde traffic from the ER to the Golgi (Mellman, supra).

In clathrin-based vesicle formation, adapter proteins bring vesicle cargo and coat proteins together at the surface of the budding membrane. Adapter protein-1 and -2 select cargo from the TGN and plasma membrane, respectively, based on molecular information encoded on the cytoplasmic tail of integral membrane cargo proteins. Adapter proteins also recruit clathrin to the bud site. Clathrin is a protein complex consisting of three large and three small polypeptide chains arranged in a three-legged structure called a triskelion. Multiple triskelions and other coat proteins appear to self-assemble on the membrane to form a coated pit. This assembly process may serve to deform the membrane into a budding vesicle. GTP-bound ADP-ribosylation factor (Arf) is also incorporated into the coated assembly. Another small G-protein, dynamin, forms a ring complex around the neck of the forming vesicle and may provide the mechanochemical force to seal the bud, thereby releasing the vesicle. The coated vesicle complex is then transported through the cytosol. During the transport process, Arf-bound GTP is hydrolyzed to GDP, and the coat dissociates from the transport vesicle (West, M.A. et al. (1997) J. Cell Biol. 138:1239-1254).

Vesicles which bud from the ER and the Golgi are covered with a protein coat similar to the clathrin coat of endocytic and TGN vesicles. The coat protein (COP) is assembled from cytosolic precursor molecules at specific budding regions on the organelle. The COP coat consists of two major components, a G-protein (Arf or Sar) and coat protomer (coatomer). Coatomer is an equimolar

complex of seven proteins, termed alpha-, beta-, beta'-, gamma-, delta-, epsilon- and zeta-COP. The coatomer complex binds to dilysine motifs contained on the cytoplasmic tails of integral membrane proteins. These include the KKXX retrieval motif of membrane proteins of the ER and dibasic/diphenylamine motifs of members of the p24 family. The p24 family of type I membrane proteins represent the major membrane proteins of COPI vesicles (Harter, C. and F.T. Wieland (1998) Proc. Natl. Acad. Sci. USA 95:11649-11654).

Organelle Associated Molecules

SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, and SEQ ID NO:63 encode, for example, organelle associated molecules.

Eukaryotic cells are organized into various cellular organelles which has the effect of separating specific molecules and their functions from one another and from the cytosol. Within the cell, various membrane structures surround and define these organelles while allowing them to interact with one another and the cell environment through both active and passive transport processes. Important cell organelles include the nucleus, the Golgi apparatus, the endoplasmic reticulum, mitochondria, peroxisomes, lysosomes, endosomes, and secretory vesicles.

Nucleus

The cell nucleus contains all of the genetic information of the cell in the form of DNA, and the components and machinery necessary for replication of DNA and for transcription of DNA into RNA. (See Alberts, B. et al. (1994) Molecular Biology of the Cell, Garland Publishing Inc., New York NY, pp. 335-399.) DNA is organized into compact structures in the nucleus by interactions with various DNA-binding proteins such as histones and non-histone chromosomal proteins. DNA-specific nucleases, DNAses, partially degrade these compacted structures prior to DNA replication or transcription. DNA replication takes place with the aid of DNA helicases which unwind the double-stranded DNA helix, and DNA polymerases that duplicate the separated DNA strands.

Transcriptional regulatory proteins are essential for the control of gene expression. Some of these proteins function as transcription factors that initiate, activate, repress, or terminate gene transcription. Transcription factors generally bind to the promoter, enhancer, and upstream regulatory regions of a gene in a sequence-specific manner, although some factors bind regulatory elements within or downstream of a gene's coding region. Transcription factors may bind to a specific region of DNA singly or as a complex with other accessory factors. (Reviewed in Lewin, B. (1990) Genes IV, Oxford University Press, New York NY, and Cell Press, Cambridge MA, pp. 554-570.) Many transcription factors incorporate DNA-binding structural motifs which comprise either α

helices or ß sheets that bind to the major groove of DNA. Four well-characterized structural motifs are helix-turn-helix, zinc finger, leucine zipper, and helix-loop-helix. Proteins containing these motifs may act alone as monomers, or they may form homo- or heterodimers that interact with DNA.

Many neoplastic disorders in humans can be attributed to inappropriate gene expression. Malignant cell growth may result from either excessive expression of tumor promoting genes or insufficient expression of tumor suppressor genes (Cleary, M.L. (1992) Cancer Surv. 15:89-104). Chromosomal translocations may also produce chimeric loci which fuse the coding sequence of one gene with the regulatory regions of a second unrelated gene. Such an arrangement likely results in inappropriate gene transcription, potentially contributing to malignancy.

In addition, the immune system responds to infection or trauma by activating a cascade of events that coordinate the progressive selection, amplification, and mobilization of cellular defense mechanisms. A complex and balanced program of gene activation and repression is involved in this process. However, hyperactivity of the immune system as a result of improper or insufficient regulation of gene expression may result in considerable tissue or organ damage. This damage is well documented in immunological responses associated with arthritis, allergens, heart attack, stroke, and infections (Isselbacher, K.J. et al. (1996) Harrison's Principles of Internal Medicine, 13/e, McGraw Hill, Inc. and Teton Data Systems Software).

Transcription of DNA into RNA also takes place in the nucleus catalyzed by RNA polymerases. Three types of RNA polymerase exist. RNA polymerase I makes large ribosomal RNAs, while RNA polymerase III makes a variety of small, stable RNAs including 5S ribosomal RNA and the transfer RNAs (tRNA). RNA polymerase II transcribes genes that will be translated into proteins. The primary transcript of RNA polymerase II is called heterogenous nuclear RNA (hnRNA), and must be further processed by splicing to remove non-coding sequences called introns. RNA splicing is mediated by small nuclear ribonucleoprotein complexes, or snRNPs, producing mature messenger RNA (mRNA) which is then transported out of the nucleus for translation into proteins.

Nucleolus

The nucleolus is a highly organized subcompartment in the nucleus that contains high concentrations of RNA and proteins and functions mainly in ribosomal RNA synthesis and assembly (Alberts, et al. supra, pp. 379-382). Ribosomal RNA (rRNA) is a structural RNA that is complexed with proteins to form ribonucleoprotein structures called ribosomes. Ribosomes provide the platform on which protein synthesis takes place.

Ribosomes are assembled in the nucleolus initially from a large, 45S rRNA combined with a variety of proteins imported from the cytoplasm, as well as smaller, 5S rRNAs. Later processing of the immature ribosome results in formation of smaller ribosomal subunits which are transported from

the nucleolus to the cytoplasm where they are assembled into functional ribosomes.

Endoplasmic Reticulum

In eukaryotes, proteins are synthesized within the endoplasmic reticulum (ER), delivered from the ER to the Golgi apparatus for post-translational processing and sorting, and transported from the Golgi to specific intracellular and extracellular destinations. Synthesis of integral membrane proteins, secreted proteins, and proteins destined for the lumen of a particular organelle occurs on the rough endoplasmic reticulum (ER). The rough ER is so named because of the rough appearance in electron micrographs imparted by the attached ribosomes on which protein synthesis proceeds. Synthesis of proteins destined for the ER actually begins in the cytosol with the synthesis of a specific signal peptide which directs the growing polypeptide and its attached ribosome to the ER membrane where the signal peptide is removed and protein synthesis is completed. Soluble proteins destined for the ER lumen, for secretion, or for transport to the lumen of other organelles pass completely into the ER lumen. Transmembrane proteins destined for the ER or for other cell membranes are translocated across the ER membrane but remain anchored in the lipid bilayer of the membrane by one or more membrane-spanning α-helical regions.

Translocated polypeptide chains destined for other organelles or for secretion also fold and assemble in the ER lumen with the aid of certain "resident" ER proteins. Protein folding in the ER is aided by two principal types of protein isomerases, protein disulfide isomerase (PDI), and peptidyl-prolyl isomerase (PPI). PDI catalyzes the oxidation of free sulfhydryl groups in cysteine residues to form intramolecular disulfide bonds in proteins. PPI, an enzyme that catalyzes the isomerization of certain proline imide bonds in oligopeptides and proteins, is considered to govern one of the rate limiting steps in the folding of many proteins to their final functional conformation. The cyclophilins represent a major class of PPI that was originally identified as the major receptor for the immunosuppressive drug cyclosporin A (Handschumacher, R.E. et al. (1984) Science 226:544-547). Molecular "chaperones" such as BiP (binding protein) in the ER recognize incorrectly folded proteins as well as proteins not yet folded into their final form and bind to them, both to prevent improper aggregation between them, and to promote proper folding.

The "N-linked" glycosylation of most soluble secreted and membrane-bound proteins by oligosacchrides linked to asparagine residues in proteins is also performed in the ER. This reaction is catalyzed by a membrane-bound enzyme, oligosaccharyl transferase.

Golgi Apparatus

The Golgi apparatus is a complex structure that lies adjacent to the ER in eukaryotic cells and serves primarily as a sorting and dispatching station for products of the ER (Alberts, et al. supra, pp. 600-610). Additional posttranslational processing, principally additional glycosylation, also occurs in

the Golgi. Indeed, the Golgi is a major site of carbohydrate synthesis, including most of the glycosaminoglycans of the extracellular matrix. N-linked oligosaccharides, added to proteins in the ER, are also further modified in the Golgi by the addition of more sugar residues to form complex N-linked oligosaccharides. "O-linked" glycosylation of proteins also occurs in the Golgi by the addition of N-acetylgalactosamine to the hydroxyl group of a serine or threonine residue followed by the sequential addition of other sugar residues to the first. This process is catalyzed by a series of glycosyltransferases each specific for a particular donor sugar nucleotide and acceptor molecule (Lodish, H. et al. (1995) Molecular Cell Biology, W.H. Freeman and Co., New York NY, pp.700-708). In many cases, both N- and O-linked oligosaccharides appear to be required for the secretion of proteins or the movement of plasma membrane glycoproteins to the cell surface.

The terminal compartment of the Golgi is the Trans-Golgi Network (TGN), where both membrane and lumenal proteins are sorted for their final destination. Transport (or secretory) vesicles destined for intracellular compartments, such as lysosomes, bud off of the TGN. Other transport vesicles bud off containing proteins destined for the plasma membrane, such as receptors, adhesion molecules, and ion channels, and secretory proteins, such as hormones, neurotransmitters, and digestive enzymes.

Vacuoles

The vacuole system is a collection of membrane bound compartments in eukaryotic cells that functions in the processes of endocytosis and exocytosis. They include phagosomes, lysosomes, endosomes, and secretory vesicles. Endocytosis is the process in cells of internalizing nutrients, solutes or small particles (pinocytosis) or large particles such as internalized receptors, viruses, bacteria, or bacterial toxins (phagocytosis). Exocytosis is the process of transporting molecules to the cell surface. It facilitates placement or localization of membrane-bound receptors or other membrane proteins and secretion of hormones, neurotransmitters, digestive enzymes, wastes, etc.

A common property of all of these vacuoles is an acidic pH environment ranging from approximately pH 4.5-5.0. This acidity is maintained by the presence of a proton ATPase that uses the energy of ATP hydrolysis to generate an electrochemical proton gradient across a membrane (Mellman, I. et al. (1986) Annu. Rev. Biochem. 55:663-700). Eukaryotic vacuolar proton ATPase (vp-ATPase) is a multimeric enzyme composed of 3-10 different subunits. One of these subunits is a highly hydrophobic polypeptide of approximately 16 kDa that is similar to the proteolipid component of vp-ATPases from eubacteria, fungi, and plant vacuoles (Mandel, M. et al. (1988) Proc. Natl. Acad. Sci. USA 85:5521-5524). The 16 kDa proteolipid component is the major subunit of the membrane portion of vp-ATPase and functions in the transport of protons across the membrane.

Lysosomes

Lysosomes are membranous vesicles containing various hydrolytic enzymes used for the controlled intracellular digestion of macromolecules. Lysosomes contain some 40 types of enzymes including proteases, nucleases, glycosidases, lipases, phospholipases, phosphatases, and sulfatases, all of which are acid hydrolases that function at a pH of about 5. Lysosomes are surrounded by a unique membrane containing transport proteins that allow the final products of macromolecule degradation, such as sugars, amino acids, and nucleotides, to be transported to the cytosol where they may be either excreted or reutilized by the cell. A vp-ATPase, such as that described above, maintains the acidic environment necessary for hydrolytic activity (Alberts, supra, pp. 610-611).

Endosomes

Endosomes are another type of acidic vacuole that is used to transport substances from the cell surface to the interior of the cell in the process of endocytosis. Like lysosomes, endosomes have an acidic environment provided by a vp-ATPase (Alberts et al. supra, pp. 610-618). Two types of endosomes are apparent based on tracer uptake studies that distinguish their time of formation in the cell and their cellular location. Early endosomes are found near the plasma membrane and appear to function primarily in the recycling of internalized receptors back to the cell surface. Late endosomes appear later in the endocytic process close to the Golgi apparatus and the nucleus, and appear to be associated with delivery of endocytosed material to lysosomes or to the TGN where they may be recycled. Specific proteins are associated with particular transport vesicles and their target compartments that may provide selectivity in targeting vesicles to their proper compartments. A cytosolic prenylated GTP-binding protein, Rab, is one such protein. Rabs 4, 5, and 11 are associated with the early endosome, whereas Rabs 7 and 9 associate with the late endosome.

Mitochondria

Mitochondria are oval-shaped organelles comprising an outer membrane, a tightly folded inner membrane, an intermembrane space between the outer and inner membranes, and a matrix inside the inner membrane. The outer membrane contains many porin molecules that allow ions and charged molecules to enter the intermembrane space, while the inner membrane contains a variety of transport proteins that transfer only selected molecules. Mitochondria are the primary sites of energy production in cells.

Energy is produced by the oxidation of glucose and fatty acids. Glucose is initially converted to pyruvate in the cytoplasm. Fatty acids and pyruvate are transported to the mitochondria for complete oxidation to CO_2 coupled by enzymes to the transport of electrons from NADH and $FADH_2$ to oxygen and to the synthesis of ATP (oxidative phosphorylation) from ADP and P_i.

Pyruvate is transported into the mitochondria and converted to acetyl-CoA for oxidation via the citric acid cycle, involving pyruvate dehydrogenase components, dihydrolipoyl transacetylase, and

dihydrolipoyl dehydrogenase. Enzymes involved in the citric acid cycle include: citrate synthetase, aconitases, isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase complex including transsuccinylases, succinyl CoA synthetase, succinate dehydrogenase, fumarases, and malate dehydrogenase. Acetyl CoA is oxidized to CO_2 with concomitant formation of NADH, $FADH_2$, and GTP. In oxidative phosphorylation, the transfer of electrons from NADH and $FADH_2$ to oxygen by dehydrogenases is coupled to the synthesis of ATP from ADP and P_i by the F_0F_1 ATPase complex in the mitochondrial inner membrane. Enzyme complexes responsible for electron transport and ATP synthesis include the F_0F_1 ATPase complex, ubiquinone(CoQ)-cytochrome c reductase, ubiquinone reductase, cytochrome b, cytochrome c_1, FeS protein, and cytochrome c oxidase.

Peroxisomes

Peroxisomes, like mitochondria, are a major site of oxygen utilization. They contain one or more enzymes, such as catalase and urate oxidase, that use molecular oxygen to remove hydrogen atoms from specific organic substrates in an oxidative reaction that produces hydrogen peroxide (Alberts, supra, pp. 574-577). Catalase oxidizes a variety of substrates including phenols, formic acid, formaldehyde, and alcohol and is important in peroxisomes of liver and kidney cells for detoxifying various toxic molecules that enter the bloodstream. Another major function of oxidative reactions in peroxisomes is the breakdown of fatty acids in a process called β oxidation. β oxidation results in shortening of the alkyl chain of fatty acids by blocks of two carbon atoms that are converted to acetyl CoA and exported to the cytosol for reuse in biosynthetic reactions.

Also like mitochondria, peroxisomes import their proteins from the cytosol using a specific signal sequence located near the C-terminus of the protein. The importance of this import process is evident in the inherited human disease Zellweger syndrome, in which a defect in importing proteins into perixosomes leads to a perixosomal deficiency resulting in severe abnormalities in the brain, liver, and kidneys, and death soon after birth. One form of this disease has been shown to be due to a mutation in the gene encoding a perixosomal integral membrane protein called peroxisome assembly factor-1.

The discovery of new human molecules satisfies a need in the art by providing new compositions which are useful in the diagnosis, study, prevention, and treatment of diseases associated with, as well as effects of exogenous compounds on, the expression of human molecules.

SUMMARY OF THE INVENTION

The present invention relates to nucleic acid sequences comprising human diagnostic and therapeutic polynucleotides (dithp) as presented in the Sequence Listing. Some of the dithp uniquely identify genes encoding human structural, functional, and regulatory molecules.

The invention provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; c) a polynucleotide sequence complementary to a); d) a polynucleotide sequence complementary to b); and e) an RNA equivalent of a) through d). In one alternative, the polynucleotide comprises a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71. In another alternative, the polynucleotide comprises at least 60 contiguous nucleotides of a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; c) a polynucleotide sequence complementary to a); d) a polynucleotide sequence complementary to b); and e) an RNA equivalent of a) through d). The invention further provides a composition for the detection of expression of human diagnostic and therapeutic polynucleotides, comprising at least one isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; c) a polynucleotide sequence complementary to a); d) a polynucleotide sequence complementary to b); and e) an RNA equivalent of a) through d); and a detectable label.

The invention also provides a method for detecting a target polynucleotide in a sample, said target polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; c) a polynucleotide sequence complementary to a); d) a polynucleotide sequence complementary to b); and e) an RNA equivalent of a) through d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof. In one alternative, the probe comprises at least 30 contiguous nucleotides. In another alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a recombinant polynucleotide comprising a promoter sequence

operably linked to an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; c) a polynucleotide sequence complementary to a); d) a polynucleotide sequence complementary to b); and e) an RNA equivalent of a) through d). In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide. In a further alternative, the invention provides a method for producing a human diagnostic and therapeutic polypeptide, the method comprising a) culturing a cell under conditions suitable for expression of the human diagnostic and therapeutic polypeptide, wherein said cell is transformed with the recombinant polynucleotide, and b) recovering the human diagnostic and therapeutic polypeptide so expressed.

The invention also provides a purified human diagnostic and therapeutic polypeptide (DITHP) encoded by at least one polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71. Additionally, the invention provides an isolated antibody which specifically binds to the human diagnostic and therapeutic polypeptide. The invention further provides a method of identifying a test compound which specifically binds to the human diagnostic and therapeutic polypeptide, the method comprising the steps of a) providing a test compound; b) combining the human diagnostic and therapeutic polypeptide with the test compound for a sufficient time and under suitable conditions for binding; and c) detecting binding of the human diagnostic and therapeutic polypeptide to the test compound, thereby identifying the test compound which specifically binds the human diagnostic and therapeutic polypeptide.

The invention further provides a microarray wherein at least one element of the microarray is an isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; c) a polynucleotide sequence complementary to a); d) a polynucleotide sequence complementary to b); and e) an RNA equivalent of a) through d). The invention also provides a method for generating a transcript image of a sample which contains polynucleotides. The method comprises a) labeling the polynucleotides of the sample, b) contacting the elements of the microarray with the labeled polynucleotides of the sample under conditions suitable for the formation of a hybridization complex, and c) quantifying the expression of the polynucleotides in the sample.

Additionally, the invention provides a method for screening a compound for effectiveness in

altering expression of a target polynucleotide, wherein said target polynucleotide comprises a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; c) a polynucleotide sequence complementary to a); d) a polynucleotide sequence complementary to b); and e) an RNA equivalent of a) through d). The method comprises a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; ii) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; ii) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71; iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv), and alternatively, the target polynucleotide comprises a fragment of a polynucleotide sequence selected from the group consisting of i-v above; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

DESCRIPTION OF THE TABLES

Table 1 shows the sequence identification numbers (SEQ ID NO:s) and template identification numbers (template IDs) corresponding to the polynucleotides of the present invention, along with their GenBank hits (GI Numbers), probability scores, and functional annotations corresponding to the GenBank hits.

Table 2 shows the sequence identification numbers (SEQ ID NO:s) and template identification numbers (template IDs) corresponding to the polynucleotides of the present invention, along with polynucleotide segments of each template sequence as defined by the indicated "start" and "stop" nucleotide positions. The reading frames of the polynucleotide segments and the Pfam hits, Pfam descriptions, and E-values corresponding to the polypeptide domains encoded by the polynucleotide segments are indicated.

Table 3 shows the sequence identification numbers (SEQ ID NO:s) and template identification numbers (template IDs) corresponding to the polynucleotides of the present invention, along with polynucleotide segments of each template sequence as defined by the indicated "start" and "stop" nucleotide positions. The reading frames of the polynucleotide segments are shown, and the polypeptides encoded by the polynucleotide segments constitute either signal peptide (SP) or transmembrane (TM) domains, as indicated.

Table 4 shows the sequence identification numbers (SEQ ID NO:s) and template identification numbers (template IDs) corresponding to the polynucleotides of the present invention, along with component sequence identification numbers (component IDs) corresponding to each template. The component sequences, which were used to assemble the template sequences, are defined by the indicated "start" and "stop" nucleotide positions along each template.

Table 5 shows the tissue distribution profiles for the templates of the invention.

Table 6 summarizes the bioinformatics tools which are useful for analysis of the polynucleotides of the present invention. The first column of Table 6 lists analytical tools, programs, and algorithms, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences).

DETAILED DESCRIPTION OF THE INVENTION

Before the nucleic acid sequences and methods are presented, it is to be understood that this invention is not limited to the particular machines, methods, and materials described. Although particular embodiments are described, machines, methods, and materials similar or equivalent to these embodiments may be used to practice the invention. The preferred machines, methods, and materials set forth are not intended to limit the scope of the invention which is limited only by the appended claims.

The singular forms "a", "an", and "the" include plural reference unless the context clearly

dictates otherwise. All technical and scientific terms have the meanings commonly understood by one of ordinary skill in the art. All publications are incorporated by reference for the purpose of describing and disclosing the cell lines, vectors, and methodologies which are presented and which might be used in connection with the invention. Nothing in the specification is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Definitions

As used herein, the lower case "dithp" refers to a nucleic acid sequence, while the upper case "DITHP" refers to an amino acid sequence encoded by dithp. A "full-length" dithp refers to a nucleic acid sequence containing the entire coding region of a gene endogenously expressed in human tissue.

"Adjuvants" are materials such as Freund's adjuvant, mineral gels (aluminum hydroxide), and surface active substances (lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol) which may be administered to increase a host's immunological response.

"Allele" refers to an alternative form of a nucleic acid sequence. Alleles result from a "mutation," a change or an alternative reading of the genetic code. Any given gene may have none, one, or many allelic forms. Mutations which give rise to alleles include deletions, additions, or substitutions of nucleotides. Each of these changes may occur alone, or in combination with the others, one or more times in a given nucleic acid sequence. The present invention encompasses allelic dithp.

"Amino acid sequence" refers to a peptide, a polypeptide, or a protein of either natural or synthetic origin. The amino acid sequence is not limited to the complete, endogenous amino acid sequence and may be a fragment, epitope, variant, or derivative of a protein expressed by a nucleic acid sequence.

"Amplification" refers to the production of additional copies of a sequence and is carried out using polymerase chain reaction (PCR) technologies well known in the art.

"Antibody" refers to intact molecules as well as to fragments thereof, such as Fab, $F(ab')_2$, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies that bind DITHP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or peptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

"Antisense sequence" refers to a sequence capable of specifically hybridizing to a target

sequence. The antisense sequence may include DNA, RNA, or any nucleic acid mimic or analog such as peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine.

"Antisense sequence" refers to a sequence capable of specifically hybridizing to a target sequence. The antisense sequence can be DNA, RNA, or any nucleic acid mimic or analog.

"Antisense technology" refers to any technology which relies on the specific hybridization of an antisense sequence to a target sequence.

A "bin" is a portion of computer memory space used by a computer program for storage of data, and bounded in such a manner that data stored in a bin may be retrieved by the program.

"Biologically active" refers to an amino acid sequence having a structural, regulatory, or biochemical function of a naturally occurring amino acid sequence.

"Clone joining" is a process for combining gene bins based upon the bins' containing sequence information from the same clone. The sequences may assemble into a primary gene transcript as well as one or more splice variants.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing (5'-A-G-T-3' pairs with its complement 3'-T-C-A-5').

A "component sequence" is a nucleic acid sequence selected by a computer program such as PHRED and used to assemble a consensus or template sequence from one or more component sequences.

A "consensus sequence" or "template sequence" is a nucleic acid sequence which has been assembled from overlapping sequences, using a computer program for fragment assembly such as the GELVIEW fragment assembly system (Genetics Computer Group (GCG), Madison WI) or using a relational database management system (RDMS).

"Conservative amino acid substitutions" are those substitutions that, when made, least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative substitutions.

Original Residue	Conservative Substitution
Ala	Gly, Ser
Arg	His, Lys
Asn	Asp, Gln, His

Asp	Asn, Glu
Cys	Ala, Ser
Gln	Asn, Glu, His
Glu	Asp, Gln, His
Gly	Ala
His	Asn, Arg, Gln, Glu
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	His, Met, Leu, Trp, Tyr
Ser	Cys, Thr
Thr	Ser, Val
Trp	Phe, Tyr
Tyr	His, Phe, Trp
Val	Ile, Leu, Thr

Conservative substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain.

"Deletion" refers to a change in either a nucleic or amino acid sequence in which at least one nucleotide or amino acid residue, respectively, is absent.

"Derivative" refers to the chemical modification of a nucleic acid sequence, such as by replacement of hydrogen by an alkyl, acyl, amino, hydroxyl, or other group.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

"E-value" refers to the statistical probability that a match between two sequences occurred by chance.

A "fragment" is a unique portion of dithp or DITHP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 10 to 1000 contiguous amino acid residues or nucleotides. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous amino acid residues or nucleotides in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50%) of a polypeptide as shown in a certain defined sequence.

Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing and the figures, may be encompassed by the present embodiments.

A fragment of dithp comprises a region of unique polynucleotide sequence that specifically identifies dithp, for example, as distinct from any other sequence in the same genome. A fragment of dithp is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish dithp from related polynucleotide sequences. The precise length of a fragment of dithp and the region of dithp to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of DITHP is encoded by a fragment of dithp. A fragment of DITHP comprises a region of unique amino acid sequence that specifically identifies DITHP. For example, a fragment of DITHP is useful as an immunogenic peptide for the development of antibodies that specifically recognize DITHP. The precise length of a fragment of DITHP and the region of DITHP to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A "full length" nucleotide sequence is one containing at least a start site for translation to a protein sequence, followed by an open reading frame and a stop site, and encoding a “full length” polypeptide.

“Hit” refers to a sequence whose annotation will be used to describe a given template. Criteria for selecting the top hit are as follows: if the template has one or more exact nucleic acid matches, the top hit is the exact match with highest percent identity. If the template has no exact matches but has significant protein hits, the top hit is the protein hit with the lowest E-value. If the template has no significant protein hits, but does have significant non-exact nucleotide hits, the top hit is the nucleotide hit with the lowest E-value.

“Homology” refers to sequence similarity either between a reference nucleic acid sequence and at least a fragment of a dithp or between a reference amino acid sequence and a fragment of a DITHP.

“Hybridization” refers to the process by which a strand of nucleotides anneals with a complementary strand through base pairing. Specific hybridization is an indication that two nucleic acid sequences share a high degree of identity. Specific hybridization complexes form under defined annealing conditions, and remain hybridized after the “washing” step. The defined hybridization conditions include the annealing conditions and the washing step(s), the latter of which is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid probes that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely

determinable and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency.

Generally, stringency of hybridization is expressed with reference to the temperature under which the wash step is carried out. Generally, such wash temperatures are selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization is well known and can be found in Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, or 55°C may be used. SSC concentration may be varied from about 0.2 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, denatured salmon sperm DNA at about 100-200 μg/ml. Useful variations on these conditions will be readily apparent to those skilled in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their resultant proteins.

Other parameters, such as temperature, salt concentration, and detergent concentration may be varied to achieve the desired stringency. Denaturants, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as RNA:DNA hybridizations. Appropriate hybridization conditions are routinely determinable by one of ordinary skill in the art.

"Immunogenic" describes the potential for a natural, recombinant, or synthetic peptide, epitope, polypeptide, or protein to induce antibody production in appropriate animals, cells, or cell lines.

"Insertion" or "addition" refers to a change in either a nucleic or amino acid sequence in which at least one nucleotide or residue, respectively, is added to the sequence.

"Labeling" refers to the covalent or noncovalent joining of a polynucleotide, polypeptide, or antibody with a reporter molecule capable of producing a detectable or measurable signal.

"Microarray" is any arrangement of nucleic acids, amino acids, antibodies, etc., on a substrate. The substrate may be a solid support such as beads, glass, paper, nitrocellulose, nylon, or an appropriate membrane.

"Linkers" are short stretches of nucleotide sequence which may be added to a vector or a dithp to create restriction endonuclease sites to facilitate cloning. "Polylinkers" are engineered to incorporate

multiple restriction enzyme sites and to provide for the use of enzymes which leave 5' or 3' overhangs (e.g., BamHI, EcoRI, and HindIII) and those which provide blunt ends (e.g., EcoRV, SnaBI, and StuI).

"Naturally occurring" refers to an endogenous polynucleotide or polypeptide that may be isolated from viruses or prokaryotic or eukaryotic cells.

"Nucleic acid sequence" refers to the specific order of nucleotides joined by phosphodiester bonds in a linear, polymeric arrangement. Depending on the number of nucleotides, the nucleic acid sequence can be considered an oligomer, oligonucleotide, or polynucleotide. The nucleic acid can be DNA, RNA, or any nucleic acid analog, such as PNA, may be of genomic or synthetic origin, may be either double-stranded or single-stranded, and can represent either the sense or antisense (complementary) strand.

"Oligomer" refers to a nucleic acid sequence of at least about 6 nucleotides and as many as about 60 nucleotides, preferably about 15 to 40 nucleotides, and most preferably between about 20 and 30 nucleotides, that may be used in hybridization or amplification technologies. Oligomers may be used as, e.g., primers for PCR, and are usually chemically synthesized.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to a DNA mimic in which nucleotide bases are attached to a pseudopeptide backbone to increase stability. PNAs, also designated antigene agents, can prevent gene expression by targeting complementary messenger RNA.

The phrases "percent identity" and "% identity", as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is

selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequence pairs.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at http://www.ncbi.nlm.nih.gov/BLAST/. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to determine alignment between a known polynucleotide sequence and other sequences on a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at http://www.ncbi.nlm.nih.gov/gorf/bl2/. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

Penalty for mismatch: -2

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 11

Filter: on

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in figures or Sequence Listings, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity", as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the hydrophobicity and acidity of the substituted residue, thus preserving the structure (and therefore function) of the folded polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalty

Gap x drop-off: 50

Expect: 10

Word Size: 3

Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in figures or Sequence Listings, may be used to describe a length over which percentage identity may be measured.

"Post-translational modification" of a DITHP may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu and the DITHP.

"Probe" refers to dithp or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the figures and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel et al.,1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge

UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

"Purified" refers to molecules, either polynucleotides or polypeptides that are isolated or separated from their natural environment and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other compounds with which they are naturally associated.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be use to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

"Regulatory element" refers to a nucleic acid sequence from nontranslated regions of a gene, and includes enhancers, promoters, introns, and 3' untranslated regions, which interact with host proteins to carry out or regulate transcription or translation.

"Reporter" molecules are chemical or biochemical moieties used for labeling a nucleic acid, an amino acid, or an antibody. They include radionuclides; enzymes; fluorescent, chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

"Sample" is used in its broadest sense. Samples may contain nucleic or amino acids, antibodies, or other materials, and may be derived from any source (e.g., bodily fluids including, but not limited to, saliva, blood, and urine; chromosome(s), organelles, or membranes isolated from a cell; genomic DNA, RNA, or cDNA in solution or bound to a substrate; and cleared cells or tissues or blots or imprints from such cells or tissues).

"Specific binding" or "specifically binding" refers to the interaction between a protein or peptide and its agonist, antibody, antagonist, or other binding partner. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

"Substitution" refers to the replacement of at least one nucleotide or amino acid by a different nucleotide or amino acid.

"Substrate" refers to any suitable rigid or semi-rigid support including, e.g., membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles or capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular tissue or cell type under given conditions at a given time.

"Transformation" refers to a process by which exogenous DNA enters a recipient cell. Transformation may occur under natural or artificial conditions using various methods well known in the art. Transformation may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method is selected based on the host cell being transformed.

"Transformants" include stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as cells which transiently express inserted DNA or RNA.

A "transgenic organism," as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization,

but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, and plants and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 25% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 30%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or even at least 98% or greater sequence identity over a certain defined length. The variant may result in "conservative" amino acid changes which do not affect structural and/or chemical properties. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

In an alternative, variants of the polynucleotides of the present invention may be generated through recombinant methods. One possible method is a DNA shuffling technique such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:259-264; and Crameri, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of DITHP, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and

selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

In a particular embodiment, cDNA sequences derived from human tissues and cell lines were aligned based on nucleotide sequence identity and assembled into "consensus" or "template" sequences which are designated by the template identification numbers (template IDs) in column 2 of Table 1. The sequence identification numbers (SEQ ID NO:s) corresponding to the template IDs are shown in column 1. The template sequences have similarity to GenBank sequences, or "hits," as designated by the GI Numbers in column 3. The statistical probability of each GenBank hit is indicated by a probability score in column 4, and the functional annotation corresponding to each GenBank hit is listed in column 5.

The invention incorporates the nucleic acid sequences of these templates as disclosed in the Sequence Listing and the use of these sequences in the diagnosis and treatment of disease states characterized by defects in human molecules. The invention further utilizes these sequences in hybridization and amplification technologies, and in particular, in technologies which assess gene expression patterns correlated with specific cells or tissues and their responses in vivo or in vitro to pharmaceutical agents, toxins, and other treatments. In this manner, the sequences of the present invention are used to develop a transcript image for a particular cell or tissue.

Derivation of Nucleic Acid Sequences

cDNA was isolated from libraries constructed using RNA derived from normal and diseased human tissues and cell lines. The human tissues and cell lines used for cDNA library construction were selected from a broad range of sources to provide a diverse population of cDNAs representative of gene

transcription throughout the human body. Descriptions of the human tissues and cell lines used for cDNA library construction are provided in the LIFESEQ database (Incyte Genomics, Inc. (Incyte), Palo Alto CA). Human tissues were broadly selected from, for example, cardiovascular, dermatologic, endocrine, gastrointestinal, hematopoietic/immune system, musculoskeletal, neural, reproductive, and urologic sources.

Cell lines used for cDNA library construction were derived from, for example, leukemic cells, teratocarcinomas, neuroepitheliomas, cervical carcinoma, lung fibroblasts, and endothelial cells. Such cell lines include, for example, THP-1, Jurkat, HUVEC, hNT2, WI38, HeLa, and other cell lines commonly used and available from public depositories (American Type Culture Collection, Manassas VA). Prior to mRNA isolation, cell lines were untreated, treated with a pharmaceutical agent such as 5'-aza-2'-deoxycytidine, treated with an activating agent such as lipopolysaccharide in the case of leukocytic cell lines, or, in the case of endothelial cell lines, subjected to shear stress.

Sequencing of the cDNAs

Methods for DNA sequencing are well known in the art. Conventional enzymatic methods employ the Klenow fragment of DNA polymerase I, SEQUENASE DNA polymerase (U.S. Biochemical Corporation, Cleveland OH), Taq polymerase (PE Biosystems, Foster City CA), thermostable T7 polymerase (Amersham Pharmacia Biotech, Inc. (Amersham Pharmacia Biotech), Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies Inc. (Life Technologies), Gaithersburg MD), to extend the nucleic acid sequence from an oligonucleotide primer annealed to the DNA template of interest. Methods have been developed for the use of both single-stranded and double-stranded templates. Chain termination reaction products may be electrophoresed on urea-polyacrylamide gels and detected either by autoradiography (for radioisotope-labeled nucleotides) or by fluorescence (for fluorophore-labeled nucleotides). Automated methods for mechanized reaction preparation, sequencing, and analysis using fluorescence detection methods have been developed. Machines used to prepare cDNAs for sequencing can include the MICROLAB 2200 liquid transfer system (Hamilton Company (Hamilton), Reno NV), Peltier thermal cycler (PTC200; MJ Research, Inc. (MJ Research), Watertown MA), and ABI CATALYST 800 thermal cycler (PE Biosystems). Sequencing can be carried out using, for example, the ABI 373 or 377 (PE Biosystems) or MEGABACE 1000 (Molecular Dynamics, Inc. (Molecular Dynamics), Sunnyvale CA) DNA sequencing systems, or other automated and manual sequencing systems well known in the art.

The nucleotide sequences of the Sequence Listing have been prepared by current, state-of-the-art, automated methods and, as such, may contain occasional sequencing errors or unidentified

nucleotides. Such unidentified nucleotides are designated by an N. These infrequent unidentified bases do not represent a hindrance to practicing the invention for those skilled in the art. Several methods employing standard recombinant techniques may be used to correct errors and complete the missing sequence information. (See, e.g., those described in Ausubel, F.M. et al. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY; and Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY.)

Assembly of cDNA Sequences

Human polynucleotide sequences may be assembled using programs or algorithms well known in the art. Sequences to be assembled are related, wholly or in part, and may be derived from a single or many different transcripts. Assembly of the sequences can be performed using such programs as PHRAP (Phils Revised Assembly Program) and the GELVIEW fragment assembly system (GCG), or other methods known in the art.

Alternatively, cDNA sequences are used as "component" sequences that are assembled into "template" or "consensus" sequences as follows. Sequence chromatograms are processed, verified, and quality scores are obtained using PHRED. Raw sequences are edited using an editing pathway known as Block 1 (See, e.g., the LIFESEQ Assembled User Guide, Incyte Genomics, Palo Alto, CA). A series of BLAST comparisons is performed and low-information segments and repetitive elements (e.g., dinucleotide repeats, Alu repeats, etc.) are replaced by "n's", or masked, to prevent spurious matches. Mitochondrial and ribosomal RNA sequences are also removed. The processed sequences are then loaded into a relational database management system (RDMS) which assigns edited sequences to existing templates, if available. When additional sequences are added into the RDMS, a process is initiated which modifies existing templates or creates new templates from works in progress (i.e., nonfinal assembled sequences) containing queued sequences or the sequences themselves. After the new sequences have been assigned to templates, the templates can be merged into bins. If multiple templates exist in one bin, the bin can be split and the templates reannotated.

Once gene bins have been generated based upon sequence alignments, bins are "clone joined" based upon clone information. Clone joining occurs when the 5' sequence of one clone is present in one bin and the 3' sequence from the same clone is present in a different bin, indicating that the two bins should be merged into a single bin. Only bins which share at least two different clones are merged.

A resultant template sequence may contain either a partial or a full length open reading frame, or all or part of a genetic regulatory element. This variation is due in part to the fact that the full length cDNAs of many genes are several hundred, and sometimes several thousand, bases in length. With current technology, cDNAs comprising the coding regions of large genes cannot be cloned because of

vector limitations, incomplete reverse transcription of the mRNA, or incomplete "second strand" synthesis. Template sequences may be extended to include additional contiguous sequences derived from the parent RNA transcript using a variety of methods known to those of skill in the art. Extension may thus be used to achieve the full length coding sequence of a gene.

Analysis of the cDNA Sequences

The cDNA sequences are analyzed using a variety of programs and algorithms which are well known in the art. (See, e.g., Ausubel, 1997, supra, Chapter 7.7; Meyers, R.A. (Ed.) (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853; and Table 6.) These analyses comprise both reading frame determinations, e.g., based on triplet codon periodicity for particular organisms (Fickett, J.W. (1982) Nucleic Acids Res. 10:5303-5318); analyses of potential start and stop codons; and homology searches.

Computer programs known to those of skill in the art for performing computer-assisted searches for amino acid and nucleic acid sequence similarity, include, for example, Basic Local Alignment Search Tool (BLAST; Altschul, S.F. (1993) J. Mol. Evol. 36:290-300; Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410). BLAST is especially useful in determining exact matches and comparing two sequence fragments of arbitrary but equal lengths, whose alignment is locally maximal and for which the alignment score meets or exceeds a threshold or cutoff score set by the user (Karlin, S. et al. (1988) Proc. Natl. Acad. Sci. USA 85:841-845). Using an appropriate search tool (e.g., BLAST or HMM), GenBank, SwissProt, BLOCKS, PFAM and other databases may be searched for sequences containing regions of homology to a query dithp or DITHP of the present invention.

Other approaches to the identification, assembly, storage, and display of nucleotide and polypeptide sequences are provided in “Relational Database for Storing Biomolecule Information,” U.S.S.N. 08/947,845, filed October 9, 1997; “Project-Based Full-Length Biomolecular Sequence Database,” U.S.S.N. 08/811,758, filed March 6, 1997; and “Relational Database and System for Storing Information Relating to Biomolecular Sequences,” U.S.S.N. 09/034,807, filed March 4, 1998, all of which are incorporated by reference herein in their entirety.

Protein hierarchies can be assigned to the putative encoded polypeptide based on, e.g., motif, BLAST, or biological analysis. Methods for assigning these hierarchies are described, for example, in “Database System Employing Protein Function Hierarchies for Viewing Biomolecular Sequence Data,” U.S.S.N. 08/812,290, filed March 6, 1997, incorporated herein by reference.

Identification of Human Diagnostic and Therapeutic Molecules Encoded by dithp

The identities of the DITHP encoded by the dithp of the present invention were obtained by analysis of the assembled cDNA sequences. SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, and SEQ ID NO:8 encode, for example, human enzyme molecules. SEQ ID NO:9 encodes, for example, an extracellular information transmission molecule. SEQ ID NO:10 and SEQ ID NO:11 encode, for example, receptor molecules. SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, and SEQ ID NO:18 encode, for example, intracellular signaling molecules. SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, and SEQ ID NO:33 encode, for example, transcription factor molecules. SEQ ID NO:34 encodes, for example, a protein modification and maintenance molecule. SEQ ID NO:35 and SEQ ID NO:36 encode, for example, nucleic acid synthesis and modification molecules. SEQ ID NO:37 encodes, for example, an antigen recognition molecule. SEQ ID NO:38 and SEQ ID NO:39 encode, for example, secreted/extracellular matrix molecules. SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, and SEQ ID NO:45 encode, for example, cytoskeletal molecules. SEQ ID NO:46, SEQ ID NO:47, and SEQ ID NO:48 encode, for example, cell membrane molecules. SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, and SEQ ID NO:53 encode, for example, ribosomal molecules. SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, and SEQ ID NO:63 encode, for example, organelle associated molecules. SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68 encode, for example, biochemical pathway molecules. SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71 encode, for example, molecules associated with growth and development.

Sequences of Human Diagnostic and Therapeutic Molecules

The dithp of the present invention may be used for a variety of diagnostic and therapeutic purposes. For example, a dithp may be used to diagnose a particular condition, disease, or disorder associated with human molecules. Such conditions, diseases, and disorders include, but are not limited to, a cell proliferative disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid,

penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder, such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; an infection caused by a viral agent classified as adenovirus, arenavirus, bunyavirus, calicivirus, coronavirus, filovirus, hepadnavirus, herpesvirus, flavivirus, orthomyxovirus, parvovirus, papovavirus, paramyxovirus, picornavirus, poxvirus, reovirus, retrovirus, rhabdovirus, or togavirus; an infection caused by a bacterial agent classified as pneumococcus, staphylococcus, streptococcus, bacillus, corynebacterium, clostridium, meningococcus, gonococcus, listeria, moraxella, kingella, haemophilus, legionella, bordetella, gram-negative enterobacterium including shigella, salmonella, or campylobacter, pseudomonas, vibrio, brucella, francisella, yersinia, bartonella, norcardium, actinomyces, mycobacterium, spirochaetale, rickettsia, chlamydia, or mycoplasma; an infection caused by a fungal agent classified as aspergillus, blastomyces, dermatophytes, cryptococcus, coccidioides, malasezzia, histoplasma, or other mycosis-causing fungal agent; and an infection caused by a parasite classified as plasmodium or malaria-causing, parasitic entamoeba, leishmania, trypanosoma, toxoplasma, pneumocystis carinii, intestinal protozoa such as giardia, trichomonas, tissue nematode such as trichinella, intestinal nematode such as ascaris, lymphatic filarial nematode, trematode such as schistosoma, and cestrode such as tapeworm; a developmental disorder such as renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea and cerebral palsy,

spina bifida, anencephaly, craniorachischisis, congenital glaucoma, cataract, and sensorineural hearing loss; an endocrine disorder such as a disorder of the hypothalamus and/or pituitary resulting from lesions such as a primary brain tumor, adenoma, infarction associated with pregnancy, hypophysectomy, aneurysm, vascular malformation, thrombosis, infection, immunological disorder, and complication due to head trauma; a disorder associated with hypopituitarism including hypogonadism, Sheehan syndrome, diabetes insipidus, Kallman's disease, Hand-Schuller-Christian disease, Letterer-Siwe disease, sarcoidosis, empty sella syndrome, and dwarfism; a disorder associated with hyperpituitarism including acromegaly, giantism, and syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) often caused by benign adenoma; a disorder associated with hypothyroidism including goiter, myxedema, acute thyroiditis associated with bacterial infection, subacute thyroiditis associated with viral infection, autoimmune thyroiditis (Hashimoto's disease), and cretinism; a disorder associated with hyperthyroidism including thyrotoxicosis and its various forms, Grave's disease, pretibial myxedema, toxic multinodular goiter, thyroid carcinoma, and Plummer's disease; a disorder associated with hyperparathyroidism including Conn disease (chronic hypercalemia); a pancreatic disorder such as Type I or Type II diabetes mellitus and associated complications; a disorder associated with the adrenals such as hyperplasia, carcinoma, or adenoma of the adrenal cortex, hypertension associated with alkalosis, amyloidosis, hypokalemia, Cushing's disease, Liddle's syndrome, and Arnold-Healy-Gordon syndrome, pheochromocytoma tumors, and Addison's disease; a disorder associated with gonadal steroid hormones such as: in women, abnormal prolactin production, infertility, endometriosis, perturbation of the menstrual cycle, polycystic ovarian disease, hyperprolactinemia, isolated gonadotropin deficiency, amenorrhea, galactorrhea, hermaphroditism, hirsutism and virilization, breast cancer, and, in post-menopausal women, osteoporosis; and, in men, Leydig cell deficiency, male climacteric phase, and germinal cell aplasia, a hypergonadal disorder associated with Leydig cell tumors, androgen resistance associated with absence of androgen receptors, syndrome of 5 α-reductase, and gynecomastia; a metabolic disorder such as Addison's disease, cerebrotendinous xanthomatosis, congenital adrenal hyperplasia, coumarin resistance, cystic fibrosis, diabetes, fatty hepatocirrhosis, fructose-1,6-diphosphatase deficiency, galactosemia, goiter, glucagonoma, glycogen storage diseases, hereditary fructose intolerance, hyperadrenalism, hypoadrenalism, hyperparathyroidism, hypoparathyroidism, hypercholesterolemia, hyperthyroidism, hypoglycemia, hypothyroidism, hyperlipidemia, hyperlipemia, lipid myopathies, lipodystrophies, lysosomal storage diseases, mannosidosis, neuraminidase deficiency, obesity, pentosuria phenylketonuria, pseudovitamin D-deficiency rickets; disorders of carbohydrate metabolism such as congenital type II dyserythropoietic anemia, diabetes, insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, fructose-1,6-diphosphatase deficiency, galactosemia,

glucagonoma, hereditary fructose intolerance, hypoglycemia, mannosidosis, neuraminidase deficiency, obesity, galactose epimerase deficiency, glycogen storage diseases, lysosomal storage diseases, fructosuria, pentosuria, and inherited abnormalities of pyruvate metabolism; disorders of lipid metabolism such as fatty liver, cholestasis, primary biliary cirrhosis, carnitine deficiency, carnitine palmitoyltransferase deficiency, myoadenylate deaminase deficiency, hypertriglyceridemia, lipid storage disorders such Fabry's disease, Gaucher's disease, Niemann-Pick's disease, metachromatic leukodystrophy, adrenoleukodystrophy, GM_2 gangliosidosis, and ceroid lipofuscinosis, abetalipoproteinemia, Tangier disease, hyperlipoproteinemia, diabetes mellitus, lipodystrophy, lipomatoses, acute panniculitis, disseminated fat necrosis, adiposis dolorosa, lipoid adrenal hyperplasia, minimal change disease, lipomas, atherosclerosis, hypercholesterolemia, hypercholesterolemia with hypertriglyceridemia, primary hypoalphalipoproteinemia, hypothyroidism, renal disease, liver disease, lecithin:cholesterol acyltransferase deficiency, cerebrotendinous xanthomatosis, sitosterolemia, hypocholesterolemia, Tay-Sachs disease, Sandhoff's disease, hyperlipidemia, hyperlipemia, lipid myopathies, and obesity; and disorders of copper metabolism such as Menke's disease, Wilson's disease, and Ehlers-Danlos syndrome type IX; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorder of the central nervous system, cerebral palsy, a neuroskeletal disorder, an autonomic nervous system disorder, a cranial nerve disorder, a spinal cord disease, muscular dystrophy and other neuromuscular disorder, a peripheral nervous system disorder, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathy, myasthenia gravis, periodic paralysis, a mental disorder including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; a gastrointestinal disorder including ulcerative colitis, gastric and duodenal ulcers, cystinuria, dibasicaminoaciduria, hypercystinuria, lysinuria, hartnup disease, tryptophan malabsorption, methionine malabsorption, histidinuria, iminoglycinuria, dicarboxylicaminoaciduria, cystinosis, renal

glycosuria, hypouricemia, familial hypophophatemic rickets, congenital chloridorrhea, distal renal tubular acidosis, Menkes' disease, Wilson's disease, lethal diarrhea, juvenile pernicious anemia, folate malabsorption, adrenoleukodystrophy, hereditary myoglobinuria, and Zellweger syndrome; a transport disorder such as akinesia, amyotrophic lateral sclerosis, ataxia telangiectasia, cystic fibrosis, Becker's muscular dystrophy, Bell's palsy, Charcot-Marie Tooth disease, diabetes mellitus, diabetes insipidus, diabetic neuropathy, Duchenne muscular dystrophy, hyperkalemic periodic paralysis, normokalemic periodic paralysis, Parkinson's disease, malignant hyperthermia, multidrug resistance, myasthenia gravis, myotonic dystrophy, catatonia, tardive dyskinesia, dystonias, peripheral neuropathy, cerebral neoplasms, prostate cancer, cardiac disorders associated with transport, e.g., angina, bradyarrythmia, tachyarrythmia, hypertension, Long QT syndrome, myocarditis, cardiomyopathy, nemaline myopathy, centronuclear myopathy, lipid myopathy, mitochondrial myopathy, thyrotoxic myopathy, ethanol myopathy, dermatomyositis, inclusion body myositis, infectious myositis, and polymyositis, neurological disorders associated with transport, e.g., Alzheimer's disease, amnesia, bipolar disorder, dementia, depression, epilepsy, Tourette's disorder, paranoid psychoses, and schizophrenia, and other disorders associated with transport, e.g., neurofibromatosis, postherpetic neuralgia, trigeminal neuropathy, sarcoidosis, sickle cell anemia, cataracts, infertility, pulmonary artery stenosis, sensorineural autosomal deafness, hyperglycemia, hypoglycemia, Grave's disease, goiter, glucose-galactose malabsorption syndrome, hypercholesterolemia, Cushing's disease, and Addison's disease; and a connective tissue disorder such as osteogenesis imperfecta, Ehlers-Danlos syndrome, chondrodysplasias, Marfan syndrome, Alport syndrome, familial aortic aneurysm, achondroplasia, mucopolysaccharidoses, osteoporosis, osteopetrosis, Paget's disease, rickets, osteomalacia, hyperparathyroidism, renal osteodystrophy, osteonecrosis, osteomyelitis, osteoma, osteoid osteoma, osteoblastoma, osteosarcoma, osteochondroma, chondroma, chondroblastoma, chondromyxoid fibroma, chondrosarcoma, fibrous cortical defect, nonossifying fibroma, fibrous dysplasia, fibrosarcoma, malignant fibrous histiocytoma, Ewing's sarcoma, primitive neuroectodermal tumor, giant cell tumor, osteoarthritis, rheumatoid arthritis, ankylosing spondyloarthritis, Reiter's syndrome, psoriatic arthritis, enteropathic arthritis, infectious arthritis, gout, gouty arthritis, calcium pyrophosphate crystal deposition disease, ganglion, synovial cyst, villonodular synovitis, systemic sclerosis, Dupuytren's contracture, hepatic fibrosis, lupus erythematosus, mixed connective tissue disease, epidermolysis bullosa simplex, bullous congenital ichthyosiform erythroderma (epidermolytic hyperkeratosis), non-epidermolytic and epidermolytic palmoplantar keratoderma, ichthyosis bullosa of Siemens, pachyonychia congenita, and white sponge nevus. The dithp can be used to detect the presence of, or to quantify the amount of, a dithp-related polynucleotide in a sample. This information is then compared to information obtained

from appropriate reference samples, and a diagnosis is established. Alternatively, a polynucleotide complementary to a given dithp can inhibit or inactivate a therapeutically relevant gene related to the dithp.

Analysis of dithp Expression Patterns

The expression of dithp may be routinely assessed by hybridization-based methods to determine, for example, the tissue-specificity, disease-specificity, or developmental stage-specificity of dithp expression. For example, the level of expression of dithp may be compared among different cell types or tissues, among diseased and normal cell types or tissues, among cell types or tissues at different developmental stages, or among cell types or tissues undergoing various treatments. This type of analysis is useful, for example, to assess the relative levels of dithp expression in fully or partially differentiated cells or tissues, to determine if changes in dithp expression levels are correlated with the development or progression of specific disease states, and to assess the response of a cell or tissue to a specific therapy, for example, in pharmacological or toxicological studies. Methods for the analysis of dithp expression are based on hybridization and amplification technologies and include membrane-based procedures such as northern blot analysis, high-throughput procedures that utilize, for example, microarrays, and PCR-based procedures.

Hybridization and Genetic Analysis

The dithp, their fragments, or complementary sequences, may be used to identify the presence of and/or to determine the degree of similarity between two (or more) nucleic acid sequences. The dithp may be hybridized to naturally occurring or recombinant nucleic acid sequences under appropriately selected temperatures and salt concentrations. Hybridization with a probe based on the nucleic acid sequence of at least one of the dithp allows for the detection of nucleic acid sequences, including genomic sequences, which are identical or related to the dithp of the Sequence Listing. Probes may be selected from non-conserved or unique regions of at least one of the polynucleotides of SEQ ID NO:1-71 and tested for their ability to identify or amplify the target nucleic acid sequence using standard protocols.

Polynucleotide sequences that are capable of hybridizing, in particular, to those shown in SEQ ID NO:1-71 and fragments thereof, can be identified using various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) Hybridization conditions are discussed in "Definitions."

A probe for use in Southern or northern hybridization may be derived from a fragment of a dithp sequence, or its complement, that is up to several hundred nucleotides in length and is either

single-stranded or double-stranded. Such probes may be hybridized in solution to biological materials such as plasmids, bacterial, yeast, or human artificial chromosomes, cleared or sectioned tissues, or to artificial substrates containing dithp. Microarrays are particularly suitable for identifying the presence of and detecting the level of expression for multiple genes of interest by examining gene expression correlated with, e.g., various stages of development, treatment with a drug or compound, or disease progression. An array analogous to a dot or slot blot may be used to arrange and link polynucleotides to the surface of a substrate using one or more of the following: mechanical (vacuum), chemical, thermal, or UV bonding procedures. Such an array may contain any number of dithp and may be produced by hand or by using available devices, materials, and machines.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

Probes may be labeled by either PCR or enzymatic techniques using a variety of commercially available reporter molecules. For example, commercial kits are available for radioactive and chemiluminescent labeling (Amersham Pharmacia Biotech) and for alkaline phosphatase labeling (Life Technologies). Alternatively, dithp may be cloned into commercially available vectors for the production of RNA probes. Such probes may be transcribed in the presence of at least one labeled nucleotide (e.g., ^{32}P-ATP, Amersham Pharmacia Biotech).

Additionally the polynucleotides of SEQ ID NO:1-71 or suitable fragments thereof can be used to isolate full length cDNA sequences utilizing hybridization and/or amplification procedures well known in the art, e.g., cDNA library screening, PCR amplification, etc. The molecular cloning of such full length cDNA sequences may employ the method of cDNA library screening with probes using the hybridization, stringency, washing, and probing strategies described above and in Ausubel, supra, Chapters 3, 5, and 6. These procedures may also be employed with genomic libraries to isolate genomic sequences of dithp in order to analyze, e.g., regulatory elements.

Genetic Mapping

Gene identification and mapping are important in the investigation and treatment of almost all conditions, diseases, and disorders. Cancer, cardiovascular disease, Alzheimer's disease, arthritis, diabetes, and mental illnesses are of particular interest. Each of these conditions is more complex than the single gene defects of sickle cell anemia or cystic fibrosis, with select groups of genes being predictive of predisposition for a particular condition, disease, or disorder. For example,

cardiovascular disease may result from malfunctioning receptor molecules that fail to clear cholesterol from the bloodstream, and diabetes may result when a particular individual's immune system is activated by an infection and attacks the insulin-producing cells of the pancreas. In some studies, Alzheimer's disease has been linked to a gene on chromosome 21; other studies predict a different gene and location. Mapping of disease genes is a complex and reiterative process and generally proceeds from genetic linkage analysis to physical mapping.

As a condition is noted among members of a family, a genetic linkage map traces parts of chromosomes that are inherited in the same pattern as the condition. Statistics link the inheritance of particular conditions to particular regions of chromosomes, as defined by RFLP or other markers. (See, for example, Lander, E. S. and Botstein, D. (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.) Occasionally, genetic markers and their locations are known from previous studies. More often, however, the markers are simply stretches of DNA that differ among individuals. Examples of genetic linkage maps can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site.

In another embodiment of the invention, dithp sequences may be used to generate hybridization probes useful in chromosomal mapping of naturally occurring genomic sequences. Either coding or noncoding sequences of dithp may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a dithp coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Meyers, supra, pp. 965-968.) Correlation between the location of dithp on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The dithp sequences may also be used to detect polymorphisms that are genetically linked to the inheritance of a particular condition, disease, or disorder.

In situ hybridization of chromosomal preparations and genetic mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending existing genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as

mouse, may reveal associated markers even if the number or arm of the corresponding human chromosome is not known. These new marker sequences can be mapped to human chromosomes and may provide valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once a disease or syndrome has been crudely correlated by genetic linkage with a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequences of the subject invention may also be used to detect differences in chromosomal architecture due to translocation, inversion, etc., among normal, carrier, or affected individuals.

Once a disease-associated gene is mapped to a chromosomal region, the gene must be cloned in order to identify mutations or other alterations (e.g., translocations or inversions) that may be correlated with disease. This process requires a physical map of the chromosomal region containing the disease-gene of interest along with associated markers. A physical map is necessary for determining the nucleotide sequence of and order of marker genes on a particular chromosomal region. Physical mapping techniques are well known in the art and require the generation of overlapping sets of cloned DNA fragments from a particular organelle, chromosome, or genome. These clones are analyzed to reconstruct and catalog their order. Once the position of a marker is determined, the DNA from that region is obtained by consulting the catalog and selecting clones from that region. The gene of interest is located through positional cloning techniques using hybridization or similar methods.

Diagnostic Uses

The dithp of the present invention may be used to design probes useful in diagnostic assays. Such assays, well known to those skilled in the art, may be used to detect or confirm conditions, disorders, or diseases associated with abnormal levels of dithp expression. Labeled probes developed from dithp sequences are added to a sample under hybridizing conditions of desired stringency. In some instances, dithp, or fragments or oligonucleotides derived from dithp, may be used as primers in amplification steps prior to hybridization. The amount of hybridization complex formed is quantified and compared with standards for that cell or tissue. If dithp expression varies significantly from the standard, the assay indicates the presence of the condition, disorder, or disease. Qualitative or quantitative diagnostic methods may include northern, dot blot, or other membrane or dip-stick based technologies or multiple-sample format technologies such as PCR, enzyme-linked immunosorbent assay (ELISA)-like, pin, or chip-based assays.

The probes described above may also be used to monitor the progress of conditions, disorders, or diseases associated with abnormal levels of dithp expression, or to evaluate the efficacy of a

particular therapeutic treatment. The candidate probe may be identified from the dithp that are specific to a given human tissue and have not been observed in GenBank or other genome databases. Such a probe may be used in animal studies, preclinical tests, clinical trials, or in monitoring the treatment of an individual patient. In a typical process, standard expression is established by methods well known in the art for use as a basis of comparison, samples from patients affected by the disorder or disease are combined with the probe to evaluate any deviation from the standard profile, and a therapeutic agent is administered and effects are monitored to generate a treatment profile. Efficacy is evaluated by determining whether the expression progresses toward or returns to the standard normal pattern. Treatment profiles may be generated over a period of several days or several months. Statistical methods well known to those skilled in the art may be use to determine the significance of such therapeutic agents.

The polynucleotides are also useful for identifying individuals from minute biological samples, for example, by matching the RFLP pattern of a sample's DNA to that of an individual's DNA. The polynucleotides of the present invention can also be used to determine the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, an individual can be identified through a unique set of DNA sequences. Once a unique ID database is established for an individual, positive identification of that individual can be made from extremely small tissue samples.

In a particular aspect, oligonucleotide primers derived from the dithp of the invention may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from dithp are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and these differences are detectable using gel electrophoresis in non-denaturing gels. In fSCCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed in silico SNP (isSNP), are capable of identifying polymorphisms by comparing the sequences of individual overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence

chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

DNA-based identification techniques are critical in forensic technology. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using, e.g., PCR, to identify individuals. (See, e.g., Erlich, H. (1992) PCR Technology, Freeman and Co., New York, NY). Similarly, polynucleotides of the present invention can be used as polymorphic markers.

There is also a need for reagents capable of identifying the source of a particular tissue. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention that are specific for particular tissues. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

The polynucleotides of the present invention can also be used as molecular weight markers on nucleic acid gels or Southern blots, as diagnostic probes for the presence of a specific mRNA in a particular cell type, in the creation of subtracted cDNA libraries which aid in the discovery of novel polynucleotides, in selection and synthesis of oligomers for attachment to an array or other support, and as an antigen to elicit an immune response.

Disease Model Systems Using dithp

The dithp of the invention or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent Number 5,175,383 and U.S. Patent Number 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

The dithp of the invention may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

The dithp of the invention can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of dithp is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress dithp, resulting, e.g., in the secretion of DITHP in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

Screening Assays

DITHP encoded by polynucleotides of the present invention may be used to screen for molecules that bind to or are bound by the encoded polypeptides. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the bound molecule. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a ligand or fragment thereof, a natural substrate, or a structural or functional mimetic. (See, Coligan et al., (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or to at least a fragment of the receptor, e.g., the active site. In either case, the molecule can be rationally designed using known techniques. Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing the polypeptide or cell membrane fractions which contain the expressed polypeptide are then contacted with a test compound and binding, stimulation, or inhibition of activity of either the polypeptide or the molecule is analyzed.

An assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. Alternatively, the assay may assess binding in the presence of a labeled competitor.

Additionally, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay using, e.g., a monoclonal or polyclonal antibody, can measure polypeptide level in a sample. The antibody can measure polypeptide level by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of the above assays can be used in a diagnostic or prognostic context. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Transcript Imaging and Toxicological Testing

Another embodiment relates to the use of dithp to develop a transcript image of a tissue or cell type. A transcript image represents the global pattern of gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by hybridizing the polynucleotides of the present invention or their complements to the totality of transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The resultant transcript image would provide a profile of gene activity pertaining to human molecules for diagnostics and therapeutics.

Transcript images which profile dithp expression may be generated using transcripts isolated from tissues, cell lines, biopsies, or other biological samples. The transcript image may thus reflect dithp expression in vivo, as in the case of a tissue or biopsy sample, or in vitro, as in the case of a cell line.

Transcript images which profile dithp expression may also be used in conjunction with in vitro model systems and preclinical evaluation of pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed molecular fingerprints or toxicant signatures, which are

indicative of mechanisms of action and toxicity (Nuwaysir, E. F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and Anderson, N. L. (2000) Toxicol. Lett. 112-113:467-71, expressly incorporated by reference herein). If a test compound has a signature similar to that of a compound with known toxicity, it is likely to share those toxic properties. These fingerprints or signatures are most useful and refined when they contain expression information from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The normalization procedure is useful for comparison of expression data after treatment with different compounds. While the assignment of gene function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released February 29, 2000, available at http://www.niehs.nih.gov/oc/news/toxchip.htm.) Therefore, it is important and desirable in toxicological screening using toxicant signatures to include all expressed gene sequences.

In one embodiment, the toxicity of a test compound is assessed by treating a biological sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples are indicative of a toxic response caused by the test compound in the treated sample.

Another particular embodiment relates to the use of DITHP encoded by polynucleotides of the present invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, are analyzed by quantifying the number of expressed proteins and their relative abundance under given conditions and at a given time. A profile of a cell's proteome may thus be generated by separating and analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, <u>supra</u>). The proteins are visualized in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is

generally proportional to the level of the protein in the sample. The optical densities of equivalently positioned protein spots from different samples, for example, from biological samples either treated or untreated with a test compound or therapeutic agent, are compared to identify any changes in protein spot density related to the treatment. The proteins in the spots are partially sequenced using, for example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry. The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In some cases, further sequence data may be obtained for definitive protein identification.

A proteomic profile may also be generated using antibodies specific for DITHP to quantify the levels of DITHP expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) Anal. Biochem. 270:103-11; Mendoze, L. G. et al. (1999) Biotechniques 27:778-88). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-reactive fluorescent compound and detecting the amount of fluorescence bound at each array element.

Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N. L. and Seilhamer, J. (1997) Electrophoresis 18:533-537), so proteome toxicant signatures may be useful in the analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins that are expressed in the treated biological sample are separated so that the amount of each protein can be quantified. The amount of each protein is compared to the amount of the corresponding protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the DITHP encoded by polynucleotides of the present invention.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the DITHP encoded by polynucleotides of the present invention. The amount of protein recognized by the antibodies is quantified. The amount of protein in the treated biological

sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample.

Transcript images may be used to profile dithp expression in distinct tissue types. This process can be used to determine human molecule activity in a particular tissue type relative to this activity in a different tissue type. Transcript images may be used to generate a profile of dithp expression characteristic of diseased tissue. Transcript images of tissues before and after treatment may be used for diagnostic purposes, to monitor the progression of disease, and to monitor the efficacy of drug treatments for diseases which affect the activity of human molecules.

Transcript images of cell lines can be used to assess human molecule activity and/or to identify cell lines that lack or misregulate this activity. Such cell lines may then be treated with pharmaceutical agents, and a transcript image following treatment may indicate the efficacy of these agents in restoring desired levels of this activity. A similar approach may be used to assess the toxicity of pharmaceutical agents as reflected by undesirable changes in human molecule activity. Candidate pharmaceutical agents may be evaluated by comparing their associated transcript images with those of pharmaceutical agents of known effectiveness.

Antisense Molecules

The polynucleotides of the present invention are useful in antisense technology. Antisense technology or therapy relies on the modulation of expression of a target protein through the specific binding of an antisense sequence to a target sequence encoding the target protein or directing its expression. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ; Alama, A. et al. (1997) Pharmacol. Res. 36(3):171-178; Crooke, S.T. (1997) Adv. Pharmacol. 40:1-49; Sharma, H.W. and R. Narayanan (1995) Bioessays 17(12):1055-1063; and Lavrosky, Y. et al. (1997) Biochem. Mol. Med. 62(1):11-22.) An antisense sequence is a polynucleotide sequence capable of specifically hybridizing to at least a portion of the target sequence. Antisense sequences bind to cellular mRNA and/or genomic DNA, affecting translation and/or transcription. Antisense sequences can be DNA, RNA, or nucleic acid mimics and analogs. (See, e.g., Rossi, J.J. et al. (1991) Antisense Res. Dev. 1(3):285-288; Lee, R. et al. (1998) Biochemistry 37(3):900-1010; Pardridge, W.M. et al. (1995) Proc. Natl. Acad. Sci. USA 92(12):5592-5596; and Nielsen, P. E. and Haaima, G. (1997) Chem. Soc. Rev. 96:73-78.) Typically, the binding which results in modulation of expression occurs through hybridization or binding of complementary base pairs. Antisense sequences can also bind to DNA duplexes through specific interactions in the major groove of the double helix.

The polynucleotides of the present invention and fragments thereof can be used as antisense sequences to modify the expression of the polypeptide encoded by dithp. The antisense sequences can be produced ex vivo, such as by using any of the ABI nucleic acid synthesizer series (PE Biosystems) or other automated systems known in the art. Antisense sequences can also be produced biologically, such as by transforming an appropriate host cell with an expression vector containing the sequence of interest. (See, e.g., Agrawal, supra.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E., et al. (1998) J. Allergy Clin. Immunol. 102(3):469-475; and Scanlon, K.J., et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) Blood 76:271; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY; Uckert, W. and W. Walther (1994) Pharmacol. Ther. 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) Br. Med. Bull. 51(1):217-225; Boado, R.J. et al. (1998) J. Pharm. Sci. 87(11):1308-1315; and Morris, M.C. et al. (1997) Nucleic Acids Res. 25(14):2730-2736.)

Expression

In order to express a biologically active DITHP, the nucleotide sequences encoding DITHP or fragments thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding DITHP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, supra, Chapters 4, 8, 16, and 17; and Ausubel, supra, Chapters 9, 10, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding DITHP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or

animal (mammalian) cell systems. (See, e.g., Sambrook, supra; Ausubel, 1995, supra, Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; Scorer, C.A. et al. (1994) Bio/Technology 12:181-184; Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, N. (1987) EMBO J. 6:307-311; Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al., (1993) Proc. Natl. Acad. Sci. USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al. (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.) The invention is not limited by the host cell employed.

For long term production of recombinant proteins in mammalian systems, stable expression of DITHP in cell lines is preferred. For example, sequences encoding DITHP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Any number of selection systems may be used to recover transformed cell lines. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.; Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14; Hartman, S.C. and R.C.Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051; Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Therapeutic Uses of dithp

The dithp of the invention may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassemias, familial hypercholesterolemia, and hemophilia resulting from Factor

VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and Somia, N. (1997) Nature 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in dithp expression or regulation causes disease, the expression of dithp from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in dithp are treated by constructing mammalian expression vectors comprising dithp and introducing these vectors by mechanical means into dithp-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and Anderson, W.F. (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and Récipon, H. (1998) Curr. Opin. Biotechnol. 9:445-450).

Expression vectors that may be effective for the expression of dithp include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). The dithp of the invention may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β-actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and Bujard, H. (1992) Proc. Natl. Acad. Sci. U.S.A. 89:5547-5551; Gossen, M. et al., (1995) Science 268:1766-1769; Rossi, F.M.V. and Blau, H.M. (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. and Blau, H.M. supra), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding DITHP from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental

parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and Eb, A.J. (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (1982) EMBO J. 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to dithp expression are treated by constructing a retrovirus vector consisting of (i) dithp under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Natl. Acad. Sci. U.S.A. 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and Miller, A.D. (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., $CD4^+$ T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020-7029; Bauer, G. et al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. U.S.A. 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver dithp to cells which have one or more genetic abnormalities with respect to the expression of dithp. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annu. Rev. Nutr. 19:511-544 and Verma, I.M. and Somia, N. (1997) Nature 18:389:239-242, both incorporated by reference herein.

In another alternative, a herpes-based, gene therapy delivery system is used to deliver dithp to target cells which have one or more genetic abnormalities with respect to the expression of dithp. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing dithp to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) Exp. Eye Res.169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W. F. et al. 1999 J. Virol. 73:519-532 and Xu, H. et al., (1994) Dev. Biol. 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver dithp to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on the SFV genome (Garoff, H. and Li, K-J. (1998) Curr. Opin. Biotech. 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full-length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting dithp into the alphavirus genome in place of the capsid-coding region results in the production of a large number of dithp RNAs and the synthesis of high levels of DITHP in vector transduced cells. While alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of dithp into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA

transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Antibodies

Anti-DITHP antibodies may be used to analyze protein expression levels. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, and Fab fragments. For descriptions of and protocols of antibody technologies, see, e.g., Pound J.D. (1998) Immunochemical Protocols, Humana Press, Totowa, NJ.

The amino acid sequence encoded by the dithp of the Sequence Listing may be analyzed by appropriate software (e.g., LASERGENE NAVIGATOR software, DNASTAR) to determine regions of high immunogenicity. The optimal sequences for immunization are selected from the C-terminus, the N-terminus, and those intervening, hydrophilic regions of the polypeptide which are likely to be exposed to the external environment when the polypeptide is in its natural conformation. Analysis used to select appropriate epitopes is also described by Ausubel (1997, supra, Chapter 11.7). Peptides used for antibody induction do not need to have biological activity; however, they must be antigenic. Peptides used to induce specific antibodies may have an amino acid sequence consisting of at five amino acids, preferably at least 10 amino acids, and most preferably 15 amino acids. A peptide which mimics an antigenic fragment of the natural polypeptide may be fused with another protein such as keyhole limpet cyanin (KLH; Sigma, St. Louis MO) for antibody production. A peptide encompassing an antigenic region may be expressed from a dithp, synthesized as described above, or purified from human cells.

Procedures well known in the art may be used for the production of antibodies. Various hosts including mice, goats, and rabbits, may be immunized by injection with a peptide. Depending on the host species, various adjuvants may be used to increase immunological response.

In one procedure, peptides about 15 residues in length may be synthesized using an ABI 431A peptide synthesizer (PE Biosystems) using fmoc-chemistry and coupled to KLH (Sigma) by reaction with M-maleimidobenzoyl-N-hydroxysuccinimide ester (Ausubel, 1995, supra). Rabbits are immunized with the peptide-KLH complex in complete Freund's adjuvant. The resulting antisera are tested for antipeptide activity by binding the peptide to plastic, blocking with 1% bovine serum albumin (BSA), reacting with rabbit antisera, washing, and reacting with radioiodinated goat anti-rabbit IgG. Antisera with antipeptide activity are tested for anti-DITHP activity using protocols well known in the art, including ELISA, radioimmunoassay (RIA), and immunoblotting.

In another procedure, isolated and purified peptide may be used to immunize mice (about 100 μg of peptide) or rabbits (about 1 mg of peptide). Subsequently, the peptide is radioiodinated and used to screen the immunized animals' B-lymphocytes for production of antipeptide antibodies. Positive

cells are then used to produce hybridomas using standard techniques. About 20 mg of peptide is sufficient for labeling and screening several thousand clones. Hybridomas of interest are detected by screening with radioiodinated peptide to identify those fusions producing peptide-specific monoclonal antibody. In a typical protocol, wells of a multi-well plate (FAST, Becton-Dickinson, Palo Alto, CA) are coated with affinity-purified, specific rabbit-anti-mouse (or suitable anti-species IgG) antibodies at 10 mg/ml. The coated wells are blocked with 1% BSA and washed and exposed to supernatants from hybridomas. After incubation, the wells are exposed to radiolabeled peptide at 1 mg/ml.

Clones producing antibodies bind a quantity of labeled peptide that is detectable above background. Such clones are expanded and subjected to 2 cycles of cloning. Cloned hybridomas are injected into pristane-treated mice to produce ascites, and monoclonal antibody is purified from the ascitic fluid by affinity chromatography on protein A (Amersham Pharmacia Biotech). Several procedures for the production of monoclonal antibodies, including in vitro production, are described in Pound (supra). Monoclonal antibodies with antipeptide activity are tested for anti-DITHP activity using protocols well known in the art, including ELISA, RIA, and immunoblotting.

Antibody fragments containing specific binding sites for an epitope may also be generated. For example, such fragments include, but are not limited to, the F(ab')2 fragments produced by pepsin digestion of the antibody molecule, and the Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, construction of Fab expression libraries in filamentous bacteriophage allows rapid and easy identification of monoclonal fragments with desired specificity (Pound, supra, Chaps. 45-47). Antibodies generated against polypeptide encoded by dithp can be used to purify and characterize full-length DITHP protein and its activity, binding partners, etc.

Assays Using Antibodies

Anti-DITHP antibodies may be used in assays to quantify the amount of DITHP found in a particular human cell. Such assays include methods utilizing the antibody and a label to detect expression level under normal or disease conditions. The peptides and antibodies of the invention may be used with or without modification or labeled by joining them, either covalently or noncovalently, with a reporter molecule.

Protocols for detecting and measuring protein expression using either polyclonal or monoclonal antibodies are well known in the art. Examples include ELISA, RIA, and fluorescent activated cell sorting (FACS). Such immunoassays typically involve the formation of complexes between the DITHP and its specific antibody and the measurement of such complexes. These and other assays are described in Pound (supra).

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 60/156,294, U.S. Ser. No. 60/155,760, U.S. Ser. No. 60/155,939, U.S. Ser. No. 60/156,565, U.S. Ser. No. 60/156,624, U.S. Ser. No. 60/156,625, U.S. Ser. No. 60/167,542, U.S. Ser. No. 60/167,522, U.S. Ser. No. 60/167,453, U.S. Ser. No. 60/167,517, U.S. Ser. No. 60/167,943, U.S. Ser. No. 60/167,945, U.S. Ser. No. 60/167,520, U.S. Ser. No. 60/168,468, U.S. Ser. No. 60/168,599, U.S. Ser. No. 60/167,410, U.S. Ser. No. 60/168,265, U.S. Ser. No. 60/168,429, U.S. Ser. No. 60/168,432, U.S. Ser. No. 60/167,521, U.S. Ser. No. 60/168,857, U.S. Ser. No. 60/168,197, U.S. Ser. No. 60/168,611, and U.S. Ser. No. 60/168,613 are hereby expressly incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from CLONTECH Laboratories, Inc. (Palo Alto CA) or isolated from various tissues. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In most cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega Corporation (Promega), Madison WI), OLIGOTEX latex particles (QIAGEN, Inc. (QIAGEN), Valencia CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Inc., Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene Cloning Systems, Inc. (Stratagene), La Jolla CA) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, Chapters 5.1 through 6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For

most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), pSPORT1 plasmid (Life Technologies), or pINCY (Incyte). Recombinant plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: the Magic or WIZARD Minipreps DNA purification system (Promega); the AGTC Miniprep purification kit (Edge BioSystems, Gaithersburg MD); and the QIAWELL 8, QIAWELL 8 Plus, and QIAWELL 8 Ultra plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit (QIAGEN). Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format. (Rao, V.B. (1994) Anal. Biochem. 216:1-14.) Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Inc. (Molecular Probes), Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 thermal cycler (PE Biosystems) or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific Corp., Sunnyvale CA) or the MICROLAB 2200 liquid transfer system (Hamilton). cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (PE Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art.

Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, Chapter 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VIII.

IV. Assembly and Analysis of Sequences

Component sequences from chromatograms were subject to PHRED analysis and assigned a quality score. The sequences having at least a required quality score were subject to various pre-processing editing pathways to eliminate, e.g., low quality 3' ends, vector and linker sequences, polyA tails, Alu repeats, mitochondrial and ribosomal sequences, bacterial contamination sequences, and sequences smaller than 50 base pairs. In particular, low-information sequences and repetitive elements (e.g., dinucleotide repeats, Alu repeats, etc.) were replaced by "n's", or masked, to prevent spurious matches.

Processed sequences were then subject to assembly procedures in which the sequences were assigned to gene bins (bins). Each sequence could only belong to one bin. Sequences in each gene bin were assembled to produce consensus sequences (templates). Subsequent new sequences were added to existing bins using BLASTn (v.1.4 WashU) and CROSSMATCH. Candidate pairs were identified as all BLAST hits having a quality score greater than or equal to 150. Alignments of at least 82% local identity were accepted into the bin. The component sequences from each bin were assembled using a version of PHRAP. Bins with several overlapping component sequences were assembled using DEEP PHRAP. The orientation (sense or antisense) of each assembled template was determined based on the number and orientation of its component sequences. Template sequences as disclosed in the sequence listing correspond to sense strand sequences (the "forward" reading frames), to the best determination. The complementary (antisense) strands are inherently disclosed herein. The component sequences which were used to assemble each template consensus sequence are listed in Table 4, along with their positions along the template nucleotide sequences.

Bins were compared against each other and those having local similarity of at least 82% were combined and reassembled. Reassembled bins having templates of insufficient overlap (less than 95% local identity) were re-split. Assembled templates were also subject to analysis by STITCHER/EXON MAPPER algorithms which analyze the probabilities of the presence of splice variants, alternatively spliced exons, splice junctions, differential expression of alternative spliced genes across tissue types or disease states, etc. These resulting bins were subject to several rounds of the above assembly procedures.

Once gene bins were generated based upon sequence alignments, bins were clone joined based upon clone information. If the 5' sequence of one clone was present in one bin and the 3' sequence from

the same clone was present in a different bin, it was likely that the two bins actually belonged together in a single bin. The resulting combined bins underwent assembly procedures to regenerate the consensus sequences.

The final assembled templates were subsequently annotated using the following procedure. Template sequences were analyzed using BLASTn (v2.0, NCBI) versus gbpri (GenBank version 118). "Hits" were defined as an exact match having from 95% local identity over 200 base pairs through 100% local identity over 100 base pairs, or a homolog match having an E-value, i.e. a probability score, of $\leq 1 \times 10^{-8}$. The hits were subject to frameshift FASTx versus GENPEPT (GenBank version 118). (See Table 6). In this analysis, a homolog match was defined as having an E-value of $\leq 1 \times 10^{-8}$. The assembly method used above was described in "System and Methods for Analyzing Biomolecular Sequences," U.S.S.N. 09/276,534, filed March 25, 1999, and the LIFESEQ Gold user manual (Incyte) both incorporated by reference herein.

Following assembly, template sequences were subjected to motif, BLAST, and functional analyses, and categorized in protein hierarchies using methods described in, e.g., "Database System Employing Protein Function Hierarchies for Viewing Biomolecular Sequence Data," U.S.S.N. 08/812,290, filed March 6, 1997; "Relational Database for Storing Biomolecule Information," U.S.S.N. 08/947,845, filed October 9, 1997; "Project-Based Full-Length Biomolecular Sequence Database," U.S.S.N. 08/811,758, filed March 6, 1997; and "Relational Database and System for Storing Information Relating to Biomolecular Sequences," U.S.S.N. 09/034,807, filed March 4, 1998, all of which are incorporated by reference herein.

The template sequences were further analyzed by translating each template in all three forward reading frames and searching each translation against the Pfam database of hidden Markov model-based protein families and domains using the HMMER software package (available to the public from Washington University School of Medicine, St. Louis MO). Regions of templates which, when translated, contain similarity to Pfam consensus sequences are reported in Table 2, along with descriptions of Pfam protein domains and families. Only those Pfam hits with an E-value of $\leq 1 \times 10^{-3}$ are reported. (See also World Wide Web site http://pfam.wustl.edu/ for detailed descriptions of Pfam protein domains and families.)

Additionally, the template sequences were translated in all three forward reading frames, and each translation was searched against hidden Markov models for signal peptide and transmembrane domains using the HMMER software package. Construction of hidden Markov models and their usage in sequence analysis has been described. (See, for example, Eddy, S.R. (1996) Curr. Opin. Str. Biol. 6:361-365.) Regions of templates which, when translated, contain similarity to signal peptide or transmembrane domain consensus sequences are reported in Table 3. Only those signal peptide or

transmembrane hits with a cutoff score of 11 bits or greater are reported. A cutoff score of 11 bits or greater corresponds to at least about 91-94% true-positives in signal peptide prediction, and at least about 75% true-positives in transmembrane domain prediction.

The results of HMMER analysis as reported in Tables 2 and 3 may support the results of BLAST analysis as reported in Table 1 or may suggest alternative or additional properties of template-encoded polypeptides not previously uncovered by BLAST or other analyses.

Template sequences are further analyzed using the bioinformatics tools listed in Table 6, or using sequence analysis software known in the art such as MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Template sequences may be further queried against public databases such as the GenBank rodent, mammalian, vertebrate, prokaryote, and eukaryote databases.

V. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score x Percent Identity}}{\text{5 x minimum \{length(Seq. 1), length(Seq. 2)\}}}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For

example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

VI. Tissue Distribution Profiling

A tissue distribution profile is determined for each template by compiling the cDNA library tissue classifications of its component cDNA sequences. Each component sequence, is derived from a cDNA library constructed from a human tissue. Each human tissue is classified into one of the following categories: cardiovascular system; connective tissue; digestive system; embryonic structures; endocrine system; exocrine glands; genitalia, female; genitalia, male; germ cells; hemic and immune system; liver; musculoskeletal system; nervous system; pancreas; respiratory system; sense organs; skin; stomatognathic system; unclassified/mixed; or urinary tract. Template sequences, component sequences, and cDNA library/tissue information are found in the LIFESEQ GOLD database (Incyte Genomics, Palo Alto CA).

Table 5 shows the tissue distribution profile for the templates of the invention. For each template, the three most frequently observed tissue categories are shown in column 3, along with the percentage of component sequences belonging to each category. Only tissue categories with percentage values of $\geq 10\%$ are shown. A tissue distribution of "widely distributed" in column 3 indicates percentage values of $<10\%$ in all tissue categories.

VII. Transcript Image Analysis

Transcript images are generated as described in Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number 5,840,484, incorporated herein by reference.

VIII. Extension of Polynucleotide Sequences and Isolation of a Full-length cDNA

Oligonucleotide primers designed using a dithp of the Sequence Listing are used to extend the nucleic acid sequence. One primer is synthesized to initiate 5' extension of the template, and the other primer, to initiate 3' extension of the template. The initial primers may be designed using OLIGO 4.06 software (National Biosciences, Inc. (National Biosciences), Plymouth MN), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations are avoided. Selected human

cDNA libraries are used to extend the sequence. If more than one extension is necessary or desired, additional or nested sets of primers are designed.

High fidelity amplification is obtained by PCR using methods well known in the art. PCR is performed in 96-well plates using the PTC-200 thermal cycler (MJ Research). The reaction mix contains DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+}, $(NH_4)_2SO_4$, and ß-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ are as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well is determined by dispensing 100 µl PICOGREEN quantitation reagent (0.25% (v/v); Molecular Probes) dissolved in 1X Tris-EDTA (TE) and 0.5 µl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Incorporated (Corning), Corning NY), allowing the DNA to bind to the reagent. The plate is scanned in a FLUOROSKAN II (Labsystems Oy) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 µl to 10 µl aliquot of the reaction mixture is analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions are successful in extending the sequence.

The extended nucleotides are desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides are separated on low concentration (0.6 to 0.8%) agarose gels, fragments are excised, and agar digested with AGAR ACE (Promega). Extended clones are religated using T4 ligase (New England Biolabs, Inc., Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells are selected on antibiotic-containing media, individual colonies are picked and cultured overnight at 37°C in 384-well plates in LB/2x carbenicillin liquid media.

The cells are lysed, and DNA is amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA is quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries are reamplified

using the same conditions as described above. Samples are diluted with 20% dimethysulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems).

In like manner, the dithp is used to obtain regulatory sequences (promoters, introns, and enhancers) using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

IX. Labeling of Probes and Southern Hybridization Analyses

Hybridization probes derived from the dithp of the Sequence Listing are employed for screening cDNAs, mRNAs, or genomic DNA. The labeling of probe nucleotides between 100 and 1000 nucleotides in length is specifically described, but essentially the same procedure may be used with larger cDNA fragments. Probe sequences are labeled at room temperature for 30 minutes using a T4 polynucleotide kinase, γ^{32}P-ATP, and 0.5X One-Phor-All Plus (Amersham Pharmacia Biotech) buffer and purified using a ProbeQuant G-50 Microcolumn (Amersham Pharmacia Biotech). The probe mixture is diluted to 10^7 dpm/µg/ml hybridization buffer and used in a typical membrane-based hybridization analysis.

The DNA is digested with a restriction endonuclease such as Eco RV and is electrophoresed through a 0.7% agarose gel. The DNA fragments are transferred from the agarose to nylon membrane (NYTRAN Plus, Schleicher & Schuell, Inc., Keene NH) using procedures specified by the manufacturer of the membrane. Prehybridization is carried out for three or more hours at 68°C, and hybridization is carried out overnight at 68°C. To remove non-specific signals, blots are sequentially washed at room temperature under increasingly stringent conditions, up to 0.1x saline sodium citrate (SSC) and 0.5% sodium dodecyl sulfate. After the blots are placed in a PHOSPHORIMAGER cassette (Molecular Dynamics) or are exposed to autoradiography film, hybridization patterns of standard and experimental lanes are compared. Essentially the same procedure is employed when screening RNA.

X. Chromosome Mapping of dithp

The cDNA sequences which were used to assemble SEQ ID NO:1-71 are compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that match SEQ ID NO:1-71 are assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as PHRAP (Table 6). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome

Research (WIGR), and Généthon are used to determine if any of the clustered sequences have been previously mapped. Inclusion of a mapped sequence in a cluster will result in the assignment of all sequences of that cluster, including its particular SEQ ID NO:, to that map location. The genetic map locations of SEQ ID NO:1-71 are described as ranges, or intervals, of human chromosomes. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters.

XI. Microarray Analysis

Probe Preparation from Tissue or Cell Samples

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and polyA$^+$ RNA is purified using the oligo (dT) cellulose method. Each polyA$^+$ RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/µl oligo-dT primer (21mer), 1X first strand buffer, 0.03 units/µl RNase inhibitor, 500 µM dATP, 500 µM dGTP, 500 µM dTTP, 40 µM dCTP, 40 µM dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng polyA$^+$ RNA with GEMBRIGHT kits (Incyte). Specific control polyA$^+$ RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA (W. Lei, unpublished). As quantitative controls, the control mRNAs at 0.002 ng, 0.02 ng, 0.2 ng, and 2 ng are diluted into reverse transcription reaction at ratios of 1:100,000, 1:10,000, 1:1000, 1:100 (w/w) to sample mRNA respectively. The control mRNAs are diluted into reverse transcription reaction at ratios of 1:3, 3:1, 1:10, 10:1, 1:25, 25:1 (w/w) to sample mRNA differential expression patterns. After incubation at 37° C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85° C to the stop the reaction and degrade the RNA. Probes are purified using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The probe is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14 µl 5X SSC/0.2% SDS.

Microarray Preparation

Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 μg. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester, PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522, incorporated herein by reference. 1 μl of the array element DNA, at an average concentration of 100 ng/μl, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford, MA) for 30 minutes at 60° C followed by washes in 0.2% SDS and distilled water as before.

Hybridization

Hybridization reactions contain 9 μl of probe mixture consisting of 0.2 μg each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The probe mixture is heated to 65° C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm^2 coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140 μl of 5x SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60° C. The arrays are washed for 10 min at 45°C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45° C in a second wash buffer (0.1X SSC), and dried.

Detection

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is

focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477, Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the probe mix at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two probes from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital (A/D) conversion board (Analog Devices, Inc., Norwood, MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

XII. Complementary Nucleic Acids

Sequences complementary to the dithp are used to detect, decrease, or inhibit expression of the naturally occurring nucleotide. The use of oligonucleotides comprising from about 15 to 30 base pairs

is typical in the art. However, smaller or larger sequence fragments can also be used. Appropriate oligonucleotides are designed from the dithp using OLIGO 4.06 software (National Biosciences) or other appropriate programs and are synthesized using methods standard in the art or ordered from a commercial supplier. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent transcription factor binding to the promoter sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding and processing of the transcript.

XIII. Expression of DITHP

Expression and purification of DITHP is accomplished using bacterial or virus-based expression systems. For expression of DITHP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express DITHP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of DITHP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding DITHP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See e.g., Engelhard, supra; and Sandig, supra.)

In most expression systems, DITHP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from DITHP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak Company, Rochester NY). 6-His, a stretch of six consecutive histidine residues, enables purification on

metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, Chapters 10 and 16). Purified DITHP obtained by these methods can be used directly in the following activity assay.

XIV. Demonstration of DITHP Activity

DITHP activity is demonstrated through a variety of specific assays, some of which are outlined below.

Oxidoreductase activity of DITHP is measured by the increase in extinction coefficient of NAD(P)H coenzyme at 340 nm for the measurement of oxidation activity, or the decrease in extinction coefficient of NAD(P)H coenzyme at 340 nm for the measurement of reduction activity (Dalziel, K. (1963) J. Biol. Chem. 238:2850-2858). One of three substrates may be used: Asn-βGal, biocytidine, or ubiquinone-10. The respective subunits of the enzyme reaction, for example, cytochtome c_1-b oxidoreductase and cytochrome c, are reconstituted. The reaction mixture contains a)1-2 mg/ml DITHP; and b) 15 mM substrate, 2.4 mM $NAD(P)^+$ in 0.1 M phosphate buffer, pH 7.1 (oxidation reaction), or 2.0 mM NAD(P)H, in 0.1 M Na_2HPO_4 buffer, pH 7.4 (reduction reaction); in a total volume of 0.1 ml. Changes in absorbance at 340 nm (A_{340}) are measured at 23.5° C using a recording spectrophotometer (Shimadzu Scientific Instruments, Inc., Pleasanton CA). The amount of NAD(P)H is stoichiometrically equivalent to the amount of substrate initially present, and the change in A_{340} is a direct measure of the amount of NAD(P)H produced; $\Delta A_{340} = 6620[NADH]$. Oxidoreductase activity of DITHP activity is proportional to the amount of NAD(P)H present in the assay.

Transferase activity of DITHP is measured through assays such as a methyl transferase assay in which the transfer of radiolabeled methyl groups between a donor substrate and an acceptor substrate is measured (Bokar, J.A. et al. (1994) J. Biol. Chem. 269:17697-17704). Reaction mixtures (50 µl final volume) contain 15 mM HEPES, pH 7.9, 1.5 mM $MgCl_2$, 10 mM dithiothreitol, 3% polyvinylalcohol, 1.5 µCi [*methyl*-^{3}H]AdoMet (0.375 µM AdoMet) (DuPont-NEN), 0.6 µg DITHP, and acceptor substrate (0.4 µg [^{35}S]RNA or 6-mercaptopurine (6-MP) to 1 mM final concentration). Reaction mixtures are incubated at 30°C for 30 minutes, then 65 °C for 5 minutes. The products are separated by chromatography or electrophoresis and the level of methyl transferase activity is determined by quantification of *methyl*-^{3}H recovery.

DITHP hydrolase activity is measured by the hydrolysis of appropriate synthetic peptide substrates conjugated with various chromogenic molecules in which the degree of hydrolysis is quantified by spectrophotometric (or fluorometric) absorption of the released chromophore. (Beynon, R.J. and J.S. Bond (1994) Proteolytic Enzymes: A Practical Approach, Oxford University Press, New York NY, pp. 25-55) Peptide substrates are designed according to the category of protease activity as

endopeptidase (serine, cysteine, aspartic proteases), animopeptidase (leucine aminopeptidase), or carboxypeptidase (Carboxypeptidase A and B, procollagen C-proteinase).

DITHP isomerase activity such as peptidyl prolyl *cis/trans* isomerase activity can be assayed by an enzyme assay described by Rahfeld, J.U., et al. (1994) (FEBS Lett. 352: 180-184). The assay is performed at 10°C in 35 mM HEPES buffer, pH 7.8, containing chymotrypsin (0.5 mg/ml) and DITHP at a variety of concentrations. Under these assay conditions, the substrate, Suc-Ala-Xaa-Pro-Phe-4-NA, is in equilibrium with respect to the prolyl bond, with 80-95% in *trans* and 5-20% in *cis* conformation. An aliquot (2 ul) of the substrate dissolved in dimethyl sulfoxide (10 mg/ml) is added to the reaction mixture described above. Only the *cis* isomer of the substrate is a substrate for cleavage by chymotrypsin. Thus, as the substrate is isomerized by DITHP, the product is cleaved by chymotrypsin to produce 4-nitroanilide, which is detected by it's absorbance at 390 nm. 4-Nitroanilide appears in a time-dependent and a DITHP concentration-dependent manner.

An assay for DITHP activity associated with growth and development measures cell proliferation as the amount of newly initiated DNA synthesis in Swiss mouse 3T3 cells. A plasmid containing polynucleotides encoding DITHP is transfected into quiescent 3T3 cultured cells using methods well known in the art. The transiently transfected cells are then incubated in the presence of [^{3}H]thymidine, a radioactive DNA precursor. Where applicable, varying amounts of DITHP ligand are added to the transfected cells. Incorporation of [^{3}H]thymidine into acid-precipitable DNA is measured over an appropriate time interval, and the amount incorporated is directly proportional to the amount of newly synthesized DNA.

Growth factor activity of DITHP is measured by the stimulation of DNA synthesis in Swiss mouse 3T3 cells (McKay, I. and I. Leigh, eds. (1993) Growth Factors: A Practical Approach, Oxford University Press, New York NY). Initiation of DNA synthesis indicates the cells' entry into the mitotic cycle and their commitment to undergo later division. 3T3 cells are competent to respond to most growth factors, not only those that are mitogenic, but also those that are involved in embryonic induction. This competence is possible because the in vivo specificity demonstrated by some growth factors is not necessarily inherent but is determined by the responding tissue. In this assay, varying amounts of DITHP are added to quiescent 3T3 cultured cells in the presence of [^{3}H]thymidine, a radioactive DNA precursor. DITHP for this assay can be obtained by recombinant means or from biochemical preparations. Incorporation of [^{3}H]thymidine into acid-precipitable DNA is measured over an appropriate time interval, and the amount incorporated is directly proportional to the amount of newly synthesized DNA. A linear dose-response curve over at least a hundred-fold DITHP concentration range is indicative of growth factor activity. One unit of activity per milliliter is defined

as the concentration of DITHP producing a 50% response level, where 100% represents maximal incorporation of [^{3}H]thymidine into acid-precipitable DNA.

Alternatively, an assay for cytokine activity of DITHP measures the proliferation of leukocytes. In this assay, the amount of tritiated thymidine incorporated into newly synthesized DNA is used to estimate proliferative activity. Varying amounts of DITHP are added to cultured leukocytes, such as granulocytes, monocytes, or lymphocytes, in the presence of [^{3}H]thymidine, a radioactive DNA precursor. DITHP for this assay can be obtained by recombinant means or from biochemical preparations. Incorporation of [^{3}H]thymidine into acid-precipitable DNA is measured over an appropriate time interval, and the amount incorporated is directly proportional to the amount of newly synthesized DNA. A linear dose-response curve over at least a hundred-fold DITHP concentration range is indicative of DITHP activity. One unit of activity per milliliter is conventionally defined as the concentration of DITHP producing a 50% response level, where 100% represents maximal incorporation of [^{3}H]thymidine into acid-precipitable DNA.

An alternative assay for DITHP cytokine activity utilizes a Boyden micro chamber (Neuroprobe, Cabin John MD) to measure leukocyte chemotaxis (Vicari, supra). In this assay, about 10^5 migratory cells such as macrophages or monocytes are placed in cell culture media in the upper compartment of the chamber. Varying dilutions of DITHP are placed in the lower compartment. The two compartments are separated by a 5 or 8 micron pore polycarbonate filter (Nucleopore, Pleasanton CA). After incubation at 37°C for 80 to 120 minutes, the filters are fixed in methanol and stained with appropriate labeling agents. Cells which migrate to the other side of the filter are counted using standard microscopy. The chemotactic index is calculated by dividing the number of migratory cells counted when DITHP is present in the lower compartment by the number of migratory cells counted when only media is present in the lower compartment. The chemotactic index is proportional to the activity of DITHP.

Alternatively, cell lines or tissues transformed with a vector containing dithp can be assayed for DITHP activity by immunoblotting. Cells are denatured in SDS in the presence of β-mercaptoethanol, nucleic acids removed by ethanol precipitation, and proteins purified by acetone precipitation. Pellets are resuspended in 20 mM tris buffer at pH 7.5 and incubated with Protein G-Sepharose pre-coated with an antibody specific for DITHP. After washing, the Sepharose beads are boiled in electrophoresis sample buffer, and the eluted proteins subjected to SDS-PAGE. The SDS-PAGE is transferred to a nitrocellulose membrane for immunoblotting, and the DITHP activity is assessed by visualizing and quantifying bands on the blot using the antibody specific for DITHP as the primary antibody and ^{125}I-labeled IgG specific for the primary antibody as the secondary antibody.

DITHP kinase activity is measured by phosphorylation of a protein substrate using γ-labeled [^{32}P]-ATP and quantitation of the incorporated radioactivity using a radioisotope counter. DITHP is incubated with the protein substrate, [^{32}P]-ATP, and an appropriate kinase buffer. The [^{32}P] incorporated into the product is separated from free [^{32}P]-ATP by electrophoresis and the incorporated [^{32}P] is counted. The amount of [^{32}P] recovered is proportional to the kinase activity of DITHP in the assay. A determination of the specific amino acid residue phosphorylated is made by phosphoamino acid analysis of the hydrolyzed protein.

In the alternative, DITHP activity is measured by the increase in cell proliferation resulting from transformation of a mammalian cell line such as COS7, HeLa or CHO with an eukaryotic expression vector encoding DITHP. Eukaryotic expression vectors are commercially available, and the techniques to introduce them into cells are well known to those skilled in the art. The cells are incubated for 48-72 hours after transformation under conditions appropriate for the cell line to allow expression of DITHP. Phase microscopy is then used to compare the mitotic index of transformed versus control cells. An increase in the mitotic index indicates DITHP activity.

In a further alternative, an assay for DITHP signaling activity is based upon the ability of GPCR family proteins to modulate G protein-activated second messenger signal transduction pathways (e.g., cAMP; Gaudin, P. et al. (1998) J. Biol. Chem. 273:4990-4996). A plasmid encoding full length DITHP is transfected into a mammalian cell line (e.g., Chinese hamster ovary (CHO) or human embryonic kidney (HEK-293) cell lines) using methods well-known in the art. Transfected cells are grown in 12-well trays in culture medium for 48 hours, then the culture medium is discarded, and the attached cells are gently washed with PBS. The cells are then incubated in culture medium with or without ligand for 30 minutes, then the medium is removed and cells lysed by treatment with 1 M perchloric acid. The cAMP levels in the lysate are measured by radioimmunoassay using methods well-known in the art. Changes in the levels of cAMP in the lysate from cells exposed to ligand compared to those without ligand are proportional to the amount of DITHP present in the transfected cells.

Alternatively, an assay for DITHP protein phosphatase activity measures the hydrolysis of P-nitrophenyl phosphate (PNPP). DITHP is incubated together with PNPP in HEPES buffer pH 7.5, in the presence of 0.1% β-mercaptoethanol at 37°C for 60 min. The reaction is stopped by the addition of 6 ml of 10 N NaOH, and the increase in light absorbance of the reaction mixture at 410 nm resulting from the hydrolysis of PNPP is measured using a spectrophotometer. The increase in light absorbance is proportional to the phosphatase activity of DITHP in the assay (Diamond, R.H. et al (1994) Mol Cell Biol 14:3752-3762).

An alternative assay measures DITHP-mediated G-protein signaling activity by monitoring the mobilization of Ca^{++} as an indicator of the signal transduction pathway stimulation. (See, e.g., Grynkievicz, G. et al. (1985) J. Biol. Chem. 260:3440; McColl, S. et al. (1993) J. Immunol. 150:4550-4555; and Aussel, C. et al. (1988) J. Immunol. 140:215-220). The assay requires preloading neutrophils or T cells with a fluorescent dye such as FURA-2 or BCECF (Universal Imaging Corp, Westchester PA) whose emission characteristics are altered by Ca^{++} binding. When the cells are exposed to one or more activating stimuli artificially (e.g., anti-CD3 antibody ligation of the T cell receptor) or physiologically (e.g., by allogeneic stimulation), Ca^{++} flux takes place. This flux can be observed and quantified by assaying the cells in a fluorometer or fluorescent activated cell sorter. Measurements of Ca^{++} flux are compared between cells in their normal state and those transfected with DITHP. Increased Ca^{++} mobilization attributable to increased DITHP concentration is proportional to DITHP activity.

DITHP transport activity is assayed by measuring uptake of labeled substrates into Xenopus laevis oocytes. Oocytes at stages V and VI are injected with DITHP mRNA (10 ng per oocyte) and incubated for 3 days at 18°C in OR2 medium (82.5mM NaCl, 2.5 mM KCl, 1mM $CaCl_2$, 1mM $MgCl_2$, 1mM Na_2HPO_4, 5 mM Hepes, 3.8 mM NaOH, 50µg/ml gentamycin, pH 7.8) to allow expression of DITHP protein. Oocytes are then transferred to standard uptake medium (100mM NaCl, 2 mM KCl, 1mM $CaCl_2$, 1mM $MgCl_2$, 10 mM Hepes/Tris pH 7.5). Uptake of various substrates (e.g., amino acids, sugars, drugs, ions, and neurotransmitters) is initiated by adding labeled substrate (e.g. radiolabeled with ^3H, fluorescently labeled with rhodamine, etc.) to the oocytes. After incubating for 30 minutes, uptake is terminated by washing the oocytes three times in Na^+-free medium, measuring the incorporated label, and comparing with controls. DITHP transport activity is proportional to the level of internalized labeled substrate.

DITHP transferase activity is demonstrated by a test for galactosyltransferase activity. This can be determined by measuring the transfer of radiolabeled galactose from UDP-galactose to a GlcNAc-terminated oligosaccharide chain (Kolbinger, F. et al. (1998) J. Biol. Chem. 273:58-65). The sample is incubated with 14 µl of assay stock solution (180 mM sodium cacodylate, pH 6.5, 1 mg/ml bovine serum albumin, 0.26 mM UDP-galactose, 2 µl of UDP-[^{3}H]galactose), 1 µl of $MnCl_2$ (500 mM), and 2.5 µl of GlcNAcβO-$(CH_2)_8$-CO_2Me (37 mg/ml in dimethyl sulfoxide) for 60 minutes at 37°C. The reaction is quenched by the addition of 1 ml of water and loaded on a C18 Sep-Pak cartridge (Waters), and the column is washed twice with 5 ml of water to remove unreacted UDP-[^{3}H]galactose. The [^{3}H]galactosylated GlcNAcβO-$(CH_2)_8$-CO_2Me remains bound to the column during the water washes and is eluted with 5 ml of methanol. Radioactivity in the eluted material is measured

by liquid scintillation counting and is proportional to galactosyltransferase activity in the starting sample.

In the alternative, DITHP induction by heat or toxins may be demonstrated using primary cultures of human fibroblasts or human cell lines such as CCL-13, HEK293, or HEP G2 (ATCC). To heat induce DITHP expression, aliquots of cells are incubated at 42 °C for 15, 30, or 60 minutes. Control aliquots are incubated at 37 °C for the same time periods. To induce DITHP expression by toxins, aliquots of cells are treated with 100 μM arsenite or 20 mM azetidine-2-carboxylic acid for 0, 3, 6, or 12 hours. After exposure to heat, arsenite, or the amino acid analogue, samples of the treated cells are harvested and cell lysates prepared for analysis by western blot. Cells are lysed in lysis buffer containing 1% Nonidet P-40, 0.15 M NaCl, 50 mM Tris-HCl, 5 mM EDTA, 2 mM N-ethylmaleimide, 2 mM phenylmethylsulfonyl fluoride, 1 mg/ml leupeptin, and 1 mg/ml pepstatin. Twenty micrograms of the cell lysate is separated on an 8% SDS-PAGE gel and transferred to a membrane. After blocking with 5% nonfat dry milk/phosphate-buffered saline for 1 h, the membrane is incubated overnight at 4^0C or at room temperature for 2-4 hours with a 1:1000 dilution of anti-DITHP serum in 2% nonfat dry milk/phosphate-buffered saline. The membrane is then washed and incubated with a 1:1000 dilution of horseradish peroxidase-conjugated goat anti-rabbit IgG in 2% dry milk/phosphate-buffered saline. After washing with 0.1% Tween 20 in phosphate-buffered saline, the DITHP protein is detected and compared to controls using chemiluminescence.

Alternatively, DITHP protease activity is measured by the hydrolysis of appropriate synthetic peptide substrates conjugated with various chromogenic molecules in which the degree of hydrolysis is quantified by spectrophotometric (or fluorometric) absorption of the released chromophore (Beynon, R.J. and J.S. Bond (1994) Proteolytic Enzymes: A Practical Approach, Oxford University Press, New York, NY, pp.25-55). Peptide substrates are designed according to the category of protease activity as endopeptidase (serine, cysteine, aspartic proteases, or metalloproteases), aminopeptidase (leucine aminopeptidase), or carboxypeptidase (carboxypeptidases A and B, procollagen C-proteinase). Commonly used chromogens are 2-naphthylamine, 4-nitroaniline, and furylacrylic acid. Assays are performed at ambient temperature and contain an aliquot of the enzyme and the appropriate substrate in a suitable buffer. Reactions are carried out in an optical cuvette, and the increase/decrease in absorbance of the chromogen released during hydrolysis of the peptide substrate is measured. The change in absorbance is proportional to the DITHP protease activity in the assay.

In the alternative, an assay for DITHP protease activity takes advantage of fluorescence resonance energy transfer (FRET) that occurs when one donor and one acceptor fluorophore with an appropriate spectral overlap are in close proximity. A flexible peptide linker containing a cleavage site specific for PRTS is fused between a red-shifted variant (RSGFP4) and a blue variant (BFP5) of

Green Fluorescent Protein. This fusion protein has spectral properties that suggest energy transfer is occurring from BFP5 to RSGFP4. When the fusion protein is incubated with DITHP, the substrate is cleaved, and the two fluorescent proteins dissociate. This is accompanied by a marked decrease in energy transfer which is quantified by comparing the emission spectra before and after the addition of DITHP (Mitra, R.D. et al (1996) Gene 173:13-17). This assay can also be performed in living cells. In this case the fluorescent substrate protein is expressed constitutively in cells and DITHP is introduced on an inducible vector so that FRET can be monitored in the presence and absence of DITHP (Sagot, I. et al (1999) FEBS Lett. 447:53-57).

A method to determine the nucleic acid binding activity of DITHP involves a polyacrylamide gel mobility-shift assay. In preparation for this assay, DITHP is expressed by transforming a mammalian cell line such as COS7, HeLa or CHO with a eukaryotic expression vector containing DITHP cDNA. The cells are incubated for 48-72 hours after transformation under conditions appropriate for the cell line to allow expression and accumulation of DITHP. Extracts containing solubilized proteins can be prepared from cells expressing DITHP by methods well known in the art. Portions of the extract containing DITHP are added to [^{32}P]-labeled RNA or DNA. Radioactive nucleic acid can be synthesized in vitro by techniques well known in the art. The mixtures are incubated at 25°C in the presence of RNase- and DNase-inhibitors under buffered conditions for 5-10 minutes. After incubation, the samples are analyzed by polyacrylamide gel electrophoresis followed by autoradiography. The presence of a band on the autoradiogram indicates the formation of a complex between DITHP and the radioactive transcript. A band of similar mobility will not be present in samples prepared using control extracts prepared from untransformed cells.

In the alternative, a method to determine the methylase activity of a DITHP measures transfer of radiolabeled methyl groups between a donor substrate and an acceptor substrate. Reaction mixtures (50 µl final volume) contain 15 mM HEPES, pH 7.9, 1.5 mM $MgCl_2$, 10 mM dithiothreitol, 3% polyvinylalcohol, 1.5 µCi [*methyl*-^{3}H]AdoMet (0.375 µM AdoMet) (DuPont-NEN), 0.6 µg DITHP, and acceptor substrate (e.g., 0.4 µg [^{35}S]RNA, or 6-mercaptopurine (6-MP) to 1 mM final concentration). Reaction mixtures are incubated at 30°C for 30 minutes, then 65°C for 5 minutes. Analysis of [*methyl*-^{3}H]RNA is as follows: 1) 50 µl of 2 x loading buffer (20 mM Tris-HCl, pH 7.6, 1 M LiCl, 1 mM EDTA, 1% sodium dodecyl sulphate (SDS)) and 50 µl oligo d(T)-cellulose (10 mg/ml in 1 x loading buffer) are added to the reaction mixture, and incubated at ambient temperature with shaking for 30 minutes. 2) Reaction mixtures are transferred to a 96-well filtration plate attached to a vacuum apparatus. 3) Each sample is washed sequentially with three 2.4 ml aliquots of 1 x oligo d(T) loading buffer containing 0.5% SDS, 0.1% SDS, or no SDS. and 4) RNA is eluted with 300 µl of water into a 96-well collection plate, transferred to scintillation vials containing liquid scintillant, and radioactivity determined. Analysis of [*methyl*-^{3}H]6-MP is as follows: 1) 500 µl 0.5 M borate buffer,

pH 10.0, and then 2.5 ml of 20% (v/v) isoamyl alcohol in toluene are added to the reaction mixtures. 2) The samples mixed by vigorous vortexing for ten seconds. 3) After centrifugation at 700g for 10 minutes, 1.5 ml of the organic phase is transferred to scintillation vials containing 0.5 ml absolute ethanol and liquid scintillant, and radioactivity determined. and 4) Results are corrected for the extraction of 6-MP into the organic phase (approximately 41%).

An assay for adhesion activity of DITHP measures the disruption of cytoskeletal filament networks upon overexpression of DITHP in cultured cell lines (Rezniczek, G.A. et al. (1998) J. Cell Biol. 141:209-225). cDNA encoding DITHP is subcloned into a mammalian expression vector that drives high levels of cDNA expression. This construct is transfected into cultured cells, such as rat kangaroo PtK2 or rat bladder carcinoma 804G cells. Actin filaments and intermediate filaments such as keratin and vimentin are visualized by immunofluorescence microscopy using antibodies and techniques well known in the art. The configuration and abundance of cytoskeletal filaments can be assessed and quantified using confocal imaging techniques. In particular, the bundling and collapse of cytoskeletal filament networks is indicative of DITHP adhesion activity.

Alternatively, an assay for DITHP activity measures the expression of DITHP on the cell surface. cDNA encoding DITHP is transfected into a non-leukocytic cell line. Cell surface proteins are labeled with biotin (de la Fuente, M.A. et al. (1997) Blood 90:2398-2405). Immunoprecipitations are performed using DITHP-specific antibodies, and immunoprecipitated samples are analyzed using SDS-PAGE and immunoblotting techniques. The ratio of labeled immunoprecipitant to unlabeled immunoprecipitant is proportional to the amount of DITHP expressed on the cell surface.

Alternatively, an assay for DITHP activity measures the amount of cell aggregation induced by overexpression of DITHP. In this assay, cultured cells such as NIH3T3 are transfected with cDNA encoding DITHP contained within a suitable mammalian expression vector under control of a strong promoter. Cotransfection with cDNA encoding a fluorescent marker protein, such as Green Fluorescent Protein (CLONTECH), is useful for identifying stable transfectants. The amount of cell agglutination, or clumping, associated with transfected cells is compared with that associated with untransfected cells. The amount of cell agglutination is a direct measure of DITHP activity.

DITHP may recognize and precipitate antigen from serum. This activity can be measured by the quantitative precipitin reaction (Golub, E.S. et al. (1987) Immunology: A Synthesis, Sinauer Associates, Sunderland MA, pages 113-115). DITHP is isotopically labeled using methods known in the art. Various serum concentrations are added to constant amounts of labeled DITHP. DITHP-antigen complexes precipitate out of solution and are collected by centrifugation. The amount of precipitable DITHP-antigen complex is proportional to the amount of radioisotope detected in the precipitate. The amount of precipitable DITHP-antigen complex is plotted against the serum

concentration. For various serum concentrations, a characteristic precipitation curve is obtained, in which the amount of precipitable DITHP-antigen complex initially increases proportionately with increasing serum concentration, peaks at the equivalence point, and then decreases proportionately with further increases in serum concentration. Thus, the amount of precipitable DITHP-antigen complex is a measure of DITHP activity which is characterized by sensitivity to both limiting and excess quantities of antigen.

A microtubule motility assay for DITHP measures motor protein activity. In this assay, recombinant DITHP is immobilized onto a glass slide or similar substrate. Taxol-stabilized bovine brain microtubules (commercially available) in a solution containing ATP and cytosolic extract are perfused onto the slide. Movement of microtubules as driven by DITHP motor activity can be visualized and quantified using video-enhanced light microscopy and image analysis techniques. DITHP motor protein activity is directly proportional to the frequency and velocity of microtubule movement.

Alternatively, an assay for DITHP measures the formation of protein filaments in vitro. A solution of DITHP at a concentration greater than the "critical concentration" for polymer assembly is applied to carbon-coated grids. Appropriate nucleation sites may be supplied in the solution. The grids are negative stained with 0.7% (w/v) aqueous uranyl acetate and examined by electron microscopy. The appearance of filaments of approximately 25 nm (microtubules), 8 nm (actin), or 10 nm (intermediate filaments) is a demonstration of protein activity.

DITHP electron transfer activity is demonstrated by oxidation or reduction of NADP. Substrates such as Asn-βGal, biocytidine, or ubiquinone-10 may be used. The reaction mixture contains 1-2 mg/ml HORP, 15 mM substrate, and 2.4 mM $NAD(P)^+$ in 0.1 M phosphate buffer, pH 7.1 (oxidation reaction), or 2.0 mM NAD(P)H, in 0.1 M Na_2HPO_4 buffer, pH 7.4 (reduction reaction); in a total volume of 0.1 ml. FAD may be included with NAD, according to methods well known in the art. Changes in absorbance are measured using a recording spectrophotometer. The amount of NAD(P)H is stoichiometrically equivalent to the amount of substrate initially present, and the change in A_{340} is a direct measure of the amount of NAD(P)H produced; $\Delta A_{340} = 6620[NADH]$. DITHP activity is proportional to the amount of NAD(P)H present in the assay. The increase in extinction coefficient of NAD(P)H coenzyme at 340 nm is a measure of oxidation activity, or the decrease in extinction coefficient of NAD(P)H coenzyme at 340 nm is a measure of reduction activity (Dalziel, K. (1963) J. Biol. Chem. 238:2850-2858).

DITHP transcription factor activity is measured by its ability to stimulate transcription of a reporter gene (Liu, H.Y. et al. (1997) EMBO J. 16:5289-5298). The assay entails the use of a well characterized reporter gene construct, $LexA_{op}$-LacZ, that consists of LexA DNA transcriptional control

elements ($LexA_{op}$) fused to sequences encoding the E. coli LacZ enzyme. The methods for constructing and expressing fusion genes, introducing them into cells, and measuring LacZ enzyme activity, are well known to those skilled in the art. Sequences encoding DITHP are cloned into a plasmid that directs the synthesis of a fusion protein, LexA-DITHP, consisting of DITHP and a DNA binding domain derived from the LexA transcription factor. The resulting plasmid, encoding a LexA-DITHP fusion protein, is introduced into yeast cells along with a plasmid containing the $LexA_{op}$-LacZ reporter gene. The amount of LacZ enzyme activity associated with LexA-DITHP transfected cells, relative to control cells, is proportional to the amount of transcription stimulated by the DITHP.

Chromatin activity of DITHP is demonstrated by measuring sensitivity to DNase I (Dawson, B.A. et al. (1989) J. Biol. Chem. 264:12830-12837). Samples are treated with DNase I, followed by insertion of a cleavable biotinylated nucleotide analog, 5-[(N-biotinamido)hexanoamido-ethyl-1,3-thiopropionyl-3-aminoallyl]-2'-deoxyuridine 5'-triphosphate using nick-repair techniques well known to those skilled in the art. Following purification and digestion with EcoRI restriction endonuclease, biotinylated sequences are affinity isolated by sequential binding to streptavidin and biotincellulose.

Another specific assay demonstrates the ion conductance capacity of DITHP using an electrophysiological assay. DITHP is expressed by transforming a mammalian cell line such as COS7, HeLa or CHO with a eukaryotic expression vector encoding DITHP. Eukaryotic expression vectors are commercially available, and the techniques to introduce them into cells are well known to those skilled in the art. A small amount of a second plasmid, which expresses any one of a number of marker genes such as β-galactosidase, is co-transformed into the cells in order to allow rapid identification of those cells which have taken up and expressed the foreign DNA. The cells are incubated for 48-72 hours after transformation under conditions appropriate for the cell line to allow expression and accumulation of DITHP and β-galactosidase. Transformed cells expressing β-galactosidase are stained blue when a suitable colorimetric substrate is added to the culture media under conditions that are well known in the art. Stained cells are tested for differences in membrane conductance due to various ions by electrophysiological techniques that are well known in the art. Untransformed cells, and/or cells transformed with either vector sequences alone or β-galactosidase sequences alone, are used as controls and tested in parallel. The contribution of DITHP to cation or anion conductance can be shown by incubating the cells using antibodies specific for either DITHP. The respective antibodies will bind to the extracellular side of DITHP, thereby blocking the pore in the ion channel, and the associated conductance.

XV. Functional Assays

DITHP function is assessed by expressing dithp at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen Corporation, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected.

Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; CLONTECH), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties.

FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of DITHP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding DITHP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Inc., Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding DITHP and other genes of interest can be analyzed by northern analysis or microarray techniques.

XVI. Production of Antibodies

DITHP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the DITHP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding peptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, Chapter 11.)

Typically, peptides 15 residues in length are synthesized using an ABI 431A peptide synthesizer (PE Biosystems) using fmoc-chemistry and coupled to KLH (Sigma) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, supra.) Rabbits are immunized with the peptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide activity by, for example, binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG. Antisera with antipeptide activity are tested for anti-DITHP activity using protocols well known in the art, including ELISA, RIA, and immunoblotting.

XVII. Purification of Naturally Occurring DITHP Using Specific Antibodies

Naturally occurring or recombinant DITHP is substantially purified by immunoaffinity chromatography using antibodies specific for DITHP. An immunoaffinity column is constructed by covalently coupling anti-DITHP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing DITHP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of DITHP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/DITHP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and DITHP is collected.

XVIII. Identification of Molecules Which Interact with DITHP

DITHP, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent. (See, e.g., Bolton, A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled DITHP, washed, and any wells with labeled DITHP complex are assayed. Data obtained using different concentrations of

DITHP are used to calculate values for the number, affinity, and association of DITHP with the candidate molecules.

Alternatively, molecules interacting with DITHP are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989) Nature 340:245-246, or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (CLONTECH).

DITHP may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the above-described modes for carrying out the invention which are obvious to those skilled in the field of molecular biology or related fields are intended to be within the scope of the following claims.

TABLE 1

SEQ ID NO:	Template ID	GI Number	Probability Score	Annotation
1	405310.1.oct	g3876615	2.30E-36	Similarity to Yeast D-lactate dehydrogenase (SW:DLD1_YEAST); cDNA EST EMBL:C12235 comes from this gene; cDNA EST EMBL:C12916 comes from this gene; cDNA EST EMBL:C10532 comes from this gene; cDNA EST EMBL:C10979 comes from this gene; cDNA EST y
2	480731.6.oct	g5669919	3.00E-92	hydroxypyruvate reductase (Homo sapiens)
3	334751.2.dec	g262476	1.80E-186	cystathionine gamma-lyase, cystathionase {possibly alternatively spliced} {EC 4.4.1.1} (human, liver, Peptide, 405 aa)
4	237330.8.dec	g7291276	5.00E-70	CG10509 gene product (Drosophila melanogaster)
5	053778.11.dec	g2905643	1.10E-49	ribitol kinase
6	360645.10.dec	g7022797	0	unnamed protein product (Homo sapiens)
7	334808.1.dec	g2789461	1.20E-244	trehalase
8	997089.7.dec	g7023108	0	Homo sapiens cDNA FLJ10830 fis, clone NT2RP4001143, weakly similar to SUCCINYL-DIAMINOPIMELATE DESUCCINYLASE (EC 3.5.1.18).
9	237152.1.dec	g3355904	3.60E-81	fibroblast growth factor (FGF-18)
10	232851.7.dec	g4098959	4.00E-16	tumor necrosis factor receptor-like gene 2 (Homo sapiens)
11	083804.1.dec	g3851699	4.60E-146	chemokine receptor
12	272721.6.oct	g7330736	6.00E-25	CDK5 activator-binding protein (Rattus norvegicus)
13	461603.4.oct	g8250239	4.00E-72	protein phosphatase 4 regulatory subunit 2 (Homo sapiens)
14	332465.2.dec	g193110	7.00E-250	esk kinase
15	445175.3.dec	g35495	2.20E-197	protein kinase C epsilon
16	980541.1.dec	g2967685	2.5e-313	serine/threonine protein phosphatase 7 catalytic subunit
17	237996.1.dec	g3598974	1.60E-18	protein tyrosine phosphatase TD14
18	243267.9.dec	g1370092	4.00E-20	kinase (Gallus gallus)
19	242082.10.dec	g286105	6.00E-18	zinc finger protein (Mus musculus)
20	019239.1.dec	g454158	2.00E-13	zinc finger protein (Mus musculus)
21	899943.1.dec	g3869259	1.00E-278	ZNF202 beta
22	443551.1.dec	g1237278	7.20E-105	zinc finger protein
23	897957.1.dec	g488557	3.40E-71	zinc finger protein ZNF137
24	900911.1.dec	g498721	1.80E-21	zinc finger protein
25	999296.1.dec	g4469277	6.50E-65	OZF
26	442286.1.dec	g5360985	7.80E-12	dJ228H13.3 (Zinc Finger Protein)
27	901978.1.dec	g2306773	1.70E-80	zinc finger protein

TABLE 1

SEQ ID NO:	Template ID	GI Number	Probability Score	Annotation
28	479346.1.dec	g5640017	1.00E-72	zinc finger protein ZFP113 (Mus musculus)
29	481750.1.dec	g1020145	1.00E-115	DNA binding protein (Homo sapiens)
30	900917.2.dec	g1049301	6.90E-09	KRAB zinc finger protein; Method: conceptual translation supplied by author
31	999415.1.dec	g186632	1.00E-31	Human Kruppel-associated box (KRAB) mRNA, partial cds, clone BRc1744.
32	900680.2.dec	g347906	1.20E-93	zinc finger protein
33	902791.3.dec	g498721	3.40E-113	zinc finger protein
34	053826.1.dec	g2943716	1.10E-123	25 kDa trypsin inhibitor
35	204932.4.dec	g2443870	2.00E-56	R27090_2 (Homo sapiens)
36	400607.19.dec	g3142300	8.60E-29	Contains similarity to pre-mRNA processing protein PRP39 gb | L29224 from S. cerevisiae.
37	444248.7.dec	g33583	2.10E-33	Ig variable region (VDJ)
38	346599.9.dec	g178848	0	Human apolipoprotein E mRNA, complete cds.
39	480344.2.dec	g190647	1.00E-143	pregnancy-specific beta-1-glycoprotein
40	411396.24.dec	g339943	9.00E-32	Human tropomyosin mRNA, complete cds.
41	302819.4.dec	g4589482	4.00E-89	KIAA0925 protein (Homo sapiens)
42	238734.2.dec	g6522736	0	dJ777L9.2 (kinesin superfamily protein (KIF)) (Homo sapiens)
43	399525.3.dec	g3879121	1.80E-34	predicted using Genefinder; Similarity to Mouse ankyrin (PIR Acc. No. S37771); cDNA EST EMBL:T01923 comes from this gene; cDNA EST EMBL:D32335 comes from this gene; cDNA EST EMBL:D32723 comes from this gene; cDNA EST EMBL:D33269 comes from thi
44	222795.6.dec	g1657837	7.40E-98	p116Rip
45	410628.5.dec	g3879156	2.30E-97	predicted using Genefinder; Similarity to Mouse ankyrin (PIR Acc. No. S37771); cDNA EST EMBL:T01923 comes from this gene; cDNA EST EMBL:D32335 comes from this gene; cDNA EST EMBL:D32723 comes from this gene; cDNA EST EMBL:D33269 comes from thi
46	053649.6.dec	g2145122	0	GT334 protein (Homo sapiens)
47	221914.2.dec	g849238	4.00E-19	similar to polyposis locus protein 1 (SP:DP1_HUMAN, Q00765)
48	347748.2.dec	g7271867	2.00E-22	golgi membrane protein GP73 (Homo sapiens)
49	401482.2.oct	g562073	0	Human ribosomal protein L35 mRNA, complete cds.
50	274551.1.oct	g36145	2.00E-59	Human mRNA for ribosomal protein S12.
51	411408.20.dec	g57115	4.10E-45	ribosomal protein L31 (AA 1-125)
52	035973.1.dec	g292440	9.00E-85	Human ribosomal protein L37 mRNA, complete cds.
53	456536.1.dec	g500654	3.00E-29	Yhr148wp
54	387807.4.oct	g7684537	1.00E-08	similar to KIAA0855; similar to BAA74878 (PID:g4240199) (Homo sapiens)

TABLE 1

SEQ ID NO:	Template ID	GI Number	Probability Score	Annotation
55	406790.3.dec	g495493	2.80E-72	heme A:farnesyltransferase
56	412420.63.dec	g3090423	1.80E-15	SA3
57	196623.3.dec	g3193336	1.00E-159	DBI-related protein (Homo sapiens)
58	427916.8.dec	g5805273	3.00E-14	RNA-binding protein alpha-CP1 (Mus musculus)
59	264633.8.dec	g3329465	0	NSD1 protein (Mus musculus)
60	337822.4.dec	g3342452	3.20E-117	PHD finger DNA binding protein isoform 1
61	902943.1.dec	g178281	0	AHNAK nucleoprotein
62	256009.2.dec	g178281	1.6e-313	AHNAK nucleoprotein
63	231892.12.dec	g6164674	1.00E-07	heterogeneous nuclear ribonucleoprotein, alternate transcript (Homo sapiens)
64	197445.1.oct	g189403	1.40E-13	oxysterol-binding protein
65	348775.1.oct	g4165269	3.00E-22	Homo sapiens SYBL1 gene, exons 6-8.
66	336239.5.dec	g5441607	3.00E-35	hypothetical protein (Canis familiaris)
67	215660.4.dec	g3861217	1.10E-34	UBIQUINONE/MENAQUINONE BIOSYNTHESIS METHLYTRANSFERASE UBIE (ubiE)
68	391940.2.dec	g4191318	0	Human 33 kDa Vamp-associated protein (VAP33) mRNA, complete cds.
69	978302.3.dec	g4530435	2.2e-312	thyroid hormone receptor-associated protein complex component TRAP80
70	228629.11.dec	g5533375	3.00E-80	cell division control protein 16 (Homo sapiens)
71	011211.5.dec	g4567068	2.30E-123	tumor suppressing STF cDNA 4

TABLE 2

SEQ ID NO:	Template ID	Start	Stop	Frame	Pfam Hit	Pfam Description	E-value
2	480731.6.oct	292	537	forward 1	2-Hacid_DH	PF00389 D-isomer specific 2-hydroxyacid de	1.80E-30
3	334751.2.dec	194	1234	forward 2	Cys_Met_Meta_PP	Cys/Met metabolism PLP-dependent enzyme	3.50E-175
3	334751.2.dec	468	1283	forward 3	Cys_Met_Meta_PP	Cys/Met metabolism PLP-dependent enzyme	1.80E-08
5	053778.11.dec	1452	1655	forward 3	FGGY	FGGY family of carbohydrate kinases	2.90E-07
7	334808.1.dec	65	1318	forward 2	Trehalase	Trehalase	8.00E-89
7	334808.1.dec	117	1676	forward 3	Trehalase	Trehalase	1.50E-51
8	997089.7.dec	193	1365	forward 1	Peptidase_M20	Peptidase family M20/M25/M40	2.50E-52
9	237152.1.dec	215	598	forward 2	FGF	Fibroblast growth factor	8.80E-52
10	232851.7.dec	421	546	forward 1	TNFR_c6	TNFR/NGFR cysteine-rich region	1.30E-11
11	083804.1.dec	265	1011	forward 1	7tm_1	7 transmembrane receptor (rhodopsin family)	9.90E-78
14	332465.2.dec	1654	2454	forward 1	pkinase	Eukaryotic protein kinase domain	3.00E-85
15	445175.3.dec	236	511	forward 2	C2	C2 domain	4.10E-12
15	445175.3.dec	941	1090	forward 2	DAG_PE-bind	Phorbol esters/diacylglycerol binding domain (C1 domain)	1.80E-25
15	445175.3.dec	1436	1651	forward 2	pkinase	Eukaryotic protein kinase domain	1.40E-11
16	980541.1.dec	817	1824	forward 1	STphosphatase	Ser/Thr protein phosphatase	6.80E-93
18	243267.9.dec	209	478	forward 2	bromodomain	Bromodomain	1.60E-44
19	242082.10.dec	40	108	forward 1	zf-C2H2	Zinc finger, C2H2 type	5.70E-04
20	019239.1.dec	553	621	forward 1	zf-C2H2	Zinc finger, C2H2 type	1.60E-06
20	019239.1.dec	251	319	forward 2	zf-C2H2	Zinc finger, C2H2 type	5.10E-06
21	899943.1.dec	1899	1967	forward 3	zf-C2H2	Zinc finger, C2H2 type	2.20E-06
22	443551.1.dec	60	128	forward 3	zf-C2H2	Zinc finger, C2H2 type	7.60E-06
22	443551.1.dec	284	352	forward 2	zf-C2H2	Zinc finger, C2H2 type	8.20E-06
23	897957.1.dec	729	797	forward 3	zf-C2H2	Zinc finger, C2H2 type	5.50E-06
24	900911.1.dec	129	320	forward 3	KRAB	KRAB box	2.00E-42
24	900911.1.dec	531	599	forward 3	zf-C2H2	Zinc finger, C2H2 type	5.00E-05
25	999296.1.dec	135	203	forward 3	zf-C2H2	Zinc finger, C2H2 type	7.30E-08
26	442286.1.dec	343	528	forward 1	KRAB	KRAB box	6.80E-37
27	901978.1.dec	246	434	forward 3	KRAB	KRAB box	1.00E-35
27	901978.1.dec	993	1061	forward 3	zf-C2H2	Zinc finger, C2H2 type	5.40E-07
28	479346.1.dec	553	741	forward 1	KRAB	KRAB box	1.60E-36
28	479346.1.dec	1399	1467	forward 1	zf-C2H2	Zinc finger, C2H2 type	5.70E-07
29	481750.1.dec	357	545	forward 3	KRAB	KRAB box	1.80E-36

TABLE 2

SEQ ID NO:	Template ID	Start	Stop	Frame	Pfam Hit	Pfam Description	E-value
29	481750.1.dec	1371	1439	forward 3	zf-C2H2	Zinc finger, C2H2 type	1.20E-06
30	900917.2.dec	319	459	forward 1	KRAB	KRAB box	5.10E-16
31	999415.1.dec	247	396	forward 1	KRAB	KRAB box	4.70E-19
32	900680.2.dec	195	383	forward 3	KRAB	KRAB box	2.30E-41
32	900680.2.dec	783	851	forward 3	zf-C2H2	Zinc finger, C2H2 type	1.10E-06
33	902791.3.dec	274	456	forward 1	KRAB	KRAB box	1.00E-19
33	902791.3.dec	867	935	forward 3	zf-C2H2	Zinc finger, C2H2 type	1.20E-06
33	902791.3.dec	641	709	forward 2	zf-C2H2	Zinc finger, C2H2 type	1.90E-06
34	053826.1.dec	831	1103	forward 3	SCP	SCP-like extracellular protein	1.10E-17
34	053826.1.dec	470	805	forward 2	SCP	SCP-like extracellular protein	2.40E-10
35	204932.4.dec	171	617	forward 3	DEAD	DEAD/DEAH box helicase	4.00E-33
35	204932.4.dec	718	963	forward 1	helicase_C	Helicases conserved C-terminal domain	4.60E-26
37	444248.7.dec	135	386	forward 3	ig	Immunoglobulin domain	4.40E-08
38	346599.9.dec	131	499	forward 2	Apolipoprotein	Apolipoprotein A1/A4/E family	6.40E-04
39	480344.2.dec	881	1030	forward 2	ig	Immunoglobulin domain	7.20E-08
41	302819.4.dec	273	392	forward 3	WD40	WD domain, G-beta repeat	3.50E-06
42	238734.2.dec	97	1233	forward 1	kinesin	Kinesin motor domain	6.00E-170
43	399525.3.dec	793	891	forward 1	ank	Ank repeat	1.10E-08
43	399525.3.dec	1415	1513	forward 2	ank	Ank repeat	1.10E-07
45	410628.5.dec	1447	1545	forward 1	ank	Ank repeat	5.00E-11
51	411408.20.dec	390	674	forward 3	Ribosomal_L31e	Ribosomal protein L31e	3.30E-64
57	196623.3.dec	143	397	forward 2	ACBP	Acyl CoA binding protein	6.10E-40
57	196623.3.dec	479	904	forward 2	ECH	Enoyl-CoA hydratase/isomerase family	6.20E-09
58	427916.8.dec	285	389	forward 3	KH-domain	KH domain	7.50E-06
59	264633.8.dec	2642	2776	forward 2	PHD	PHD-finger	2.00E-07
59	264633.8.dec	2780	3010	forward 2	PWWP	PWWP domain	1.90E-20
59	264633.8.dec	948	1178	forward 3	PWWP	PWWP domain	3.20E-14
59	264633.8.dec	3317	3709	forward 2	SET	SET domain	2.50E-43
63	231892.12.dec	418	612	forward 1	rrm	RNA recognition motif. (a.k.a. RRM, RBD, or RNP domain)	4.70E-14
64	197445.1.oct	243	530	forward 3	PH	PF00169 PH (pleckstrin homology) domain	7.20E-15
64	197445.1.oct	243	530	forward 3	PH	PF00169 PH (pleckstrin homology) domain	7.20E-15
67	215660.4.dec	184	993	forward 1	Ubie_methyltran	ubiE/COQ5 methyltransferase family	1.30E-121

TABLE 3

SEQ ID NO:	Template ID	Start	Stop	Frame	Domain Type
1	405310.1.oct	1091	1159	forward 2	SP
1	405310.1.oct	1027	1089	forward 1	SP
1	405310.1.oct	2079	2150	forward 3	TM
1	405310.1.oct	1217	1276	forward 2	SP
1	405310.1.oct	1094	1165	forward 2	TM
1	405310.1.oct	2062	2151	forward 1	SP
1	405310.1.oct	2919	2972	forward 3	TM
1	405310.1.oct	2732	2788	forward 2	TM
1	405310.1.oct	1076	1135	forward 2	TM
1	405310.1.oct	2246	2302	forward 2	TM
1	405310.1.oct	1419	1487	forward 3	SP
1	405310.1.oct	2952	3020	forward 3	TM
1	405310.1.oct	2086	2154	forward 1	SP
1	405310.1.oct	2934	2993	forward 3	TM
1	405310.1.oct	2940	3020	forward 3	TM
1	405310.1.oct	887	955	forward 2	SP
1	405310.1.oct	2934	2996	forward 3	TM
1	405310.1.oct	1091	1159	forward 2	SP
1	405310.1.oct	1027	1089	forward 1	SP
1	405310.1.oct	2079	2150	forward 3	TM
1	405310.1.oct	1217	1276	forward 2	SP
1	405310.1.oct	1094	1165	forward 2	TM
1	405310.1.oct	2062	2151	forward 1	SP
1	405310.1.oct	2919	2972	forward 3	TM
1	405310.1.oct	2732	2788	forward 2	TM
1	405310.1.oct	1076	1135	forward 2	TM
1	405310.1.oct	2246	2302	forward 2	TM
1	405310.1.oct	1419	1487	forward 3	SP
1	405310.1.oct	2952	3020	forward 3	TM
1	405310.1.oct	2086	2154	forward 1	SP
1	405310.1.oct	2934	2993	forward 3	TM
1	405310.1.oct	2940	3020	forward 3	TM
1	405310.1.oct	887	955	forward 2	SP
1	405310.1.oct	2934	2996	forward 3	TM
3	334751.2.dec	1476	1532	forward 3	TM
3	334751.2.dec	675	731	forward 3	SP
3	334751.2.dec	1532	1606	forward 2	SP
3	334751.2.dec	2	85	forward 2	SP
3	334751.2.dec	795	857	forward 3	SP
3	334751.2.dec	675	737	forward 3	SP
3	334751.2.dec	1625	1681	forward 2	TM
3	334751.2.dec	783	857	forward 3	SP
4	237330.8.dec	683	730	forward 2	SP
5	053778.11.dec	1627	1686	forward 1	SP
5	053778.11.dec	1306	1374	forward 1	SP
5	053778.11.dec	1594	1686	forward 1	SP
5	053778.11.dec	1279	1374	forward 1	SP
6	360645.10.dec	385	453	forward 1	SP
6	360645.10.dec	415	495	forward 1	SP
7	334808.1.dec	529	609	forward 1	SP

TABLE 3

SEQ ID NO:	Template ID	Start	Stop	Frame	Domain Type
7	334808.1.dec	1734	1817	forward 3	SP
7	334808..1.dec	56	106	forward 2	SP
7	334808.1.dec	56	112	forward 2	SP
7	334808.1.dec	56	130	forward 2	SP
7	334808.1.dec	56	124	forward 2	SP
7	334808.1.dec	56	118	forward 2	SP
10	232851.7.dec	987	1052	forward 3	TM
10	232851.7.dec	993	1043	forward 3	TM
10	232851.7.dec	987	1043	forward 3	TM
11	083804.1.dec	841	897	forward 1	TM
11	083804.1.dec	565	630	forward 1	SP
11	083804.1.dec	706	786	forward 1	TM
11	083804.1.dec	235	303	forward 1	TM
11	083804.1.dec	829	882	forward 1	TM
11	083804.1.dec	218	274	forward 2	SP
11	083804.1.dec	244	303	forward 1	TM
11	083804.1.dec	968	1039	forward 2	SP
11	083804.1.dec	439	522	forward 1	TM
11	083804.1.dec	565	648	forward 1	SP
11	083804.1.dec	829	900	forward 1	TM
11	083804.1.dec	197	289	forward 2	SP
11	083804.1.dec	218	298	forward 2	SP
11	083804.1.dec	238	291	forward 1	TM
11	083804.1.dec	218	277	forward 2	SP
11	083804.1.dec	730	789	forward 1	TM
11	083804.1.dec	247	309	forward 1	TM
11	083804.1.dec	959	1045	forward 2	SP
12	272721.6.oct	3078	3149	forward 3	SP
12	272721.6.oct	936	992	forward 3	TM
12	272721.6.oct	1027	1086	forward 1	TM
13	461603.4.oct	2291	2359	forward 2	TM
13	461603.4.oct	2309	2356	forward 2	TM
14	332465.2.dec	2826	2882	forward 3	SP
14	332465.2.dec	2657	2719	forward 2	TM
19	242082.10.dec	1840	1923	forward 1	SP
20	019239.1.dec	2043	2123	forward 3	TM
21	899943.1.dec	3543	3617	forward 3	SP
21	899943.1.dec	3530	3610	forward 2	SP
21	899943.1.dec	2824	2877	forward 1	TM
21	899943.1.dec	3321	3380	forward 3	SP
21	899943.1.dec	3543	3602	forward 3	SP
21	899943.1.dec	2836	2892	forward 1	TM
27	901978.1.dec	1250	1309	forward 2	SP
28	479346.1.dec	467	553	forward 2	SP
29	481750.1.dec	664	717	forward 1	SP
32	900680.2.dec	27	77	forward 3	TM
34	053826.1.dec	179	253	forward 2	TM
34	053826.1.dec	1354	1416	forward 1	SP
34	053826.1.dec	1354	1416	forward 1	TM
34	053826.1.dec	1351	1401	forward 1	TM

TABLE 3

SEQ ID NO:	Template ID	Start	Stop	Frame	Domain Type
34	053826.1.dec	485	556	forward 2	SP
34	053826.1.dec	485	547	forward 2	SP
34	053826.1.dec	1250	1324	forward 2	TM
34	053826.1.dec	194	271	forward 2	TM
34	053826.1.dec	485	541	forward 2	SP
34	053826.1.dec	173	226	forward 2	TM
34	053826.1.dec	485	550	forward 2	SP
34	053826.1.dec	1363	1422	forward 1	TM
34	053826.1.dec	194	253	forward 2	TM
36	400607.19.dec	1192	1248	forward 1	TM
36	400607.19.dec	1198	1248	forward 1	TM
36	400607.19.dec	1174	1245	forward 1	TM
37	444248.7.dec	36	98	forward 3	SP
37	444248.7.dec	36	83	forward 3	SP
37	444248.7.dec	15	92	forward 3	SP
37	444248.7.dec	15	92	forward 3	SP
37	444248.7.dec	36	92	forward 3	SP
38	346599.9.dec	122	181	forward 2	SP
38	346599.9.dec	128	172	forward 2	SP
38	346599.9.dec	128	196	forward 2	SP
38	346599.9.dec	128	181	forward 2	SP
39	480344.2.dec	1105	1158	forward 1	TM
39	480344.2.dec	122	223	forward 2	SP
40	411396.24.dec	1347	1403	forward 3	SP
40	411396.24.dec	1347	1412	forward 3	SP
40	411396.24.dec	1347	1409	forward 3	SP
41	302819.4.dec	2612	2680	forward 2	SP
42	238734.2.dec	1532	1597	forward 2	SP
43	399525.3.dec	1235	1285	forward 2	SP
45	410628.5.dec	1388	1438	forward 2	TM
45	410628.5.dec	209	274	forward 2	SP
45	410628.5.dec	235	318	forward 1	SP
46	053649.6.dec	6042	6116	forward 3	TM
46	053649.6.dec	4699	4755	forward 1	TM
46	053649.6.dec	4025	4105	forward 2	TM
46	053649.6.dec	4684	4734	forward 1	TM
46	053649.6.dec	6676	6726	forward 1	TM
46	053649.6.dec	4702	4776	forward 1	TM
46	053649.6.dec	6688	6735	forward 1	SP
46	053649.6.dec	3060	3122	forward 3	TM
46	053649.6.dec	6088	6138	forward 1	TM
47	221914.2.dec	430	483	forward 1	TM
47	221914.2.dec	932	979	forward 2	SP
47	221914.2.dec	544	597	forward 1	SP
47	221914.2.dec	430	501	forward 1	SP
47	221914.2.dec	544	603	forward 1	TM
47	221914.2.dec	442	495	forward 1	SP
47	221914.2.dec	430	495	forward 1	SP
48	347748.2.dec	345	389	forward 3	SP
48	347748.2.dec	315	389	forward 3	SP

TABLE 3

SEQ ID NO:	Template ID	Start	Stop	Frame	Domain Type
48	347748.2.dec	333	389	forward 3	SP
48	347748.2.dec	351	410	forward 3	TM
48	347748.2.dec	324	389	forward 3	SP
48	347748.2.dec	330	398	forward 3	TM
48	347748.2.dec	327	389	forward 3	SP
48	347748.2.dec	342	392	forward 3	TM
48	347748.2.dec	303	389	forward 3	SP
48	347748.2.dec	333	395	forward 3	TM
51	411408.20.dec	372	422	forward 3	SP
51	411408.20.dec	661	732	forward 1	SP
51	411408.20.dec	369	434	forward 3	SP
51	411408.20.dec	318	428	forward 3	SP
51	411408.20.dec	369	428	forward 3	SP
51	411408.20.dec	369	422	forward 3	SP
52	035973.1.dec	138	224	forward 3	SP
54	387807.4.oct	469	543	forward 1	SP
54	387807.4.oct	346	396	forward 1	SP
54	387807.4.oct	346	402	forward 1	SP
54	387807.4.oct	56	148	forward 2	SP
55	406790.3.dec	792	854	forward 3	TM
57	196623.3.dec	737	808	forward 2	TM
59	264633.8.dec	5524	5583	forward 1	SP
59	264633.8.dec	5209	5277	forward 1	TM
59	264633.8.dec	5195	5248	forward 2	TM
59	264633.8.dec	4877	4939	forward 2	TM
59	264633.8.dec	5178	5249	forward 3	TM
59	264633.8.dec	7156	7218	forward 1	SP
59	264633.8.dec	5203	5280	forward 1	TM
59	264633.8.dec	6597	6647	forward 3	TM
59	264633.8.dec	703	759	forward 1	TM
59	264633.8.dec	5186	5260	forward 2	TM
59	264633.8.dec	5544	5618	forward 3	SP
59	264633.8.dec	5204	5263	forward 2	TM
59	264633.8.dec	5218	5277	forward 1	TM
59	264633.8.dec	4877	4933	forward 2	TM
60	337822.4.dec	1461	1532	forward 3	SP
60	337822.4.dec	209	286	forward 2	TM
60	337822.4.dec	210	281	forward 3	TM
62	256009.2.dec	6728	6790	forward 2	SP
62	256009.2.dec	1974	2033	forward 3	SP
62	256009.2.dec	1317	1409	forward 3	SP
62	256009.2.dec	3693	3746	forward 3	TM
63	231892.12.dec	1009	1071	forward 1	TM
63	231892.12.dec	467	556	forward 2	SP
63	231892.12.dec	985	1056	forward 1	TM
64	197445.1.oct	2155	2217	forward 1	TM
64	197445.1.oct	2146	2196	forward 1	TM
64	197445.1.oct	2380	2436	forward 1	TM
64	197445.1.oct	2158	2214	forward 1	TM
64	197445.1.oct	2155	2217	forward 1	TM

TABLE 3

SEQ ID NO:	Template ID	Start	Stop	Frame	Domain Type
64	197445.1.oct	2146	2196	forward 1	TM
64	197445.1.oct	2380	2436	forward 1	TM
64	197445.1.oct	2158	2214	forward 1	TM
65	348775.1.oct	232	288	forward 1	TM
65	348775.1.oct	937	999	forward 1	TM
65	348775.1.oct	253	306	forward 1	SP
65	348775.1.oct	1523	1582	forward 2	TM
65	348775.1.oct	942	1010	forward 3	TM
65	348775.1.oct	989	1048	forward 2	TM
65	348775.1.oct	235	282	forward 1	TM
65	348775.1.oct	967	1017	forward 1	TM
65	348775.1.oct	907	975	forward 1	TM
66	336239.5.dec	1670	1744	forward 2	SP
66	336239.5.dec	1317	1379	forward 3	TM
66	336239.5.dec	2417	2485	forward 2	SP
66	336239.5.dec	1217	1279	forward 2	TM
66	336239.5.dec	2217	2282	forward 3	SP
66	336239.5.dec	1725	1784	forward 3	TM
66	336239.5.dec	2211	2273	forward 3	TM
66	336239.5.dec	852	935	forward 3	TM
66	336239.5.dec	2226	2276	forward 3	TM
68	391940.2.dec	2125	2211	forward 1	SP
69	978302.3.dec	2319	2372	forward 3	TM
70	228629.11.dec	917	979	forward 2	TM
70	228629.11.dec	944	997	forward 2	TM
70	228629.11.dec	917	1009	forward 2	SP
71	011211.5.dec	1515	1580	forward 3	SP
71	011211.5.dec	1515	1586	forward 3	SP
71	011211.5.dec	1515	1598	forward 3	SP
71	011211.5.dec	1515	1577	forward 3	SP

Table 4

SEQ ID NO:	Template ID	Component ID	Start	Stop	SEQ ID NO:	Template ID	Component ID	Start	Stop
1	405310.1.oct	410151H1	1	211	1	405310.1.oct	g2115162	1882	2117
1	405310.1.oct	5392348H1	142	379	1	405310.1.oct	g2877111	1896	2109
1	405310.1.oct	5486608H1	242	484	1	405310.1.oct	4876648H1	1898	2038
1	405310.1.oct	2435181H1	389	625	1	405310.1.oct	626104H1	1903	2146
1	405310.1.oct	5194023H1	404	563	1	405310.1.oct	1833293H1	1936	2102
1	405310.1.oct	5184118H1	404	649	1	405310.1.oct	4215846H1	1939	2098
1	405310.1.oct	4504865H1	399	650	1	405310.1.oct	4702761H1	1975	2227
1	405310.1.oct	5677166H1	1600	1654	1	405310.1.oct	3593593H1	1988	2295
1	405310.1.oct	g2525894	1533	1654	1	405310.1.oct	5272056H1	1996	2248
1	405310.1.oct	4128628H1	1600	1681	1	405310.1.oct	3523585H1	2021	2102
1	405310.1.oct	1494882H1	1534	1654	1	405310.1.oct	3112863H1	2039	2323
1	405310.1.oct	1867328H1	1603	1654	1	405310.1.oct	1670574H1	2082	2282
1	405310.1.oct	1867591H1	1603	1654	1	405310.1.oct	1670638F6	2082	2635
1	405310.1.oct	4007319H1	1615	1684	1	405310.1.oct	1670638H1	2082	2314
1	405310.1.oct	g1195786	1654	2102	1	405310.1.oct	3135544H1	2121	2382
1	405310.1.oct	g4078042	1657	2109	1	405310.1.oct	748992H1	2175	2417
1	405310.1.oct	5704240H1	1552	1654	1	405310.1.oct	3322490H1	2175	2435
1	405310.1.oct	1905111T6	1670	2064	1	405310.1.oct	2430370H1	2261	2450
1	405310.1.oct	2452004T6	1671	2064	1	405310.1.oct	3133191H1	2320	2585
1	405310.1.oct	3720904H1	1671	1831	1	405310.1.oct	769462H1	2339	2556
1	405310.1.oct	1905111F6	1677	2102	1	405310.1.oct	5151412H1	2371	2455
1	405310.1.oct	1905111H1	1677	1944	1	405310.1.oct	1921573H1	2392	2663
1	405310.1.oct	716050H1	1552	1654	1	405310.1.oct	g1517034	2464	2749
1	405310.1.oct	g865579	1677	2014	1	405310.1.oct	2272758H1	2470	2701
1	405310.1.oct	3253763H1	1676	1923	1	405310.1.oct	g836413	2490	2856
1	405310.1.oct	3522354H1	1679	1905	1	405310.1.oct	4942363H1	2510	2782
1	405310.1.oct	2703160H1	1681	1745	1	405310.1.oct	5570061H1	2596	2790
1	405310.1.oct	835422H1	1681	1767	1	405310.1.oct	5568056H1	2596	2832
1	405310.1.oct	5704432H1	1552	1654	1	405310.1.oct	4106821H1	2599	2873
1	405310.1.oct	1783049H1	1681	1768	1	405310.1.oct	1670638T6	2643	3169
1	405310.1.oct	3423108H1	1681	1810	1	405310.1.oct	958627H1	2645	2928
1	405310.1.oct	2896508H1	1683	1882	1	405310.1.oct	958627R6	2645	3124
1	405310.1.oct	149167H1	1553	1673	1	405310.1.oct	958627T6	2645	3171
1	405310.1.oct	g4072834	1691	2102	1	405310.1.oct	3727895H1	2721	3002
1	405310.1.oct	2911475H1	1692	1886	1	405310.1.oct	4209155H1	2728	2997
1	405310.1.oct	g4187331	1693	2106	1	405310.1.oct	4318706H1	2734	3022
1	405310.1.oct	g4089320	1554	1654	1	405310.1.oct	3730224H1	2748	3041
1	405310.1.oct	g3700844	1693	2109	1	405310.1.oct	3727895T1	2773	3189
1	405310.1.oct	g2900790	1565	1654	1	405310.1.oct	g2880876	2791	3217
1	405310.1.oct	4651002H1	1719	1910	1	405310.1.oct	5493990H1	2796	3059
1	405310.1.oct	g3896271	1720	2104	1	405310.1.oct	2558339H1	2801	2960
1	405310.1.oct	3318258H1	1724	1991	1	405310.1.oct	1546674H1	2815	3012
1	405310.1.oct	g2553217	1566	1654	1	405310.1.oct	g3804535	2843	3217
1	405310.1.oct	2943433H1	1731	2016	1	405310.1.oct	g1163748	2850	3210
1	405310.1.oct	5223241H1	1746	2026	1	405310.1.oct	g1517033	2853	3210
1	405310.1.oct	g1239155	1574	1703	1	405310.1.oct	g1693600	2879	3210
1	405310.1.oct	292818H1	1747	2076	1	405310.1.oct	2571458H1	2900	3155
1	405310.1.oct	g1687172	1751	2046	1	405310.1.oct	5898551H1	2901	3178
1	405310.1.oct	4711255H1	1751	2002	1	405310.1.oct	5895283H1	2901	3188
1	405310.1.oct	g1693699	1751	2139	1	405310.1.oct	3379601H1	2951	3211
1	405310.1.oct	2769236H1	1771	1998	1	405310.1.oct	g395843	3036	3209
1	405310.1.oct	1973096H1	1772	1948	1	405310.1.oct	5118304H1	436	722
1	405310.1.oct	4935563H1	1576	1654	1	405310.1.oct	4270574H1	442	692
1	405310.1.oct	4176157H1	1770	2047	1	405310.1.oct	4548805H1	442	714
1	405310.1.oct	1927291H1	1776	1953	1	405310.1.oct	4550621H1	442	690
1	405310.1.oct	g2156621	1776	2105	1	405310.1.oct	2927758H2	404	509
1	405310.1.oct	2075838H1	1784	2033	1	405310.1.oct	g1750493	444	817
1	405310.1.oct	g2408853	1796	2105	1	405310.1.oct	4888637H1	405	685
1	405310.1.oct	g2525343	1799	2110	1	405310.1.oct	3138852H1	446	706
1	405310.1.oct	2409983H1	1813	2038	1	405310.1.oct	1352316F6	446	886
1	405310.1.oct	g2280202	1846	1985	1	405310.1.oct	1352316F1	446	959
1	405310.1.oct	3138101H1	1589	1654	1	405310.1.oct	6380007H1	446	734
1	405310.1.oct	g2819423	1859	2102	1	405310.1.oct	1352316H1	446	714

Table 4

1	405310.1.oct	6074745H1	405	706
1	405310.1.oct	039251H1	451	669
1	405310.1.oct	5121253H1	450	695
1	405310.1.oct	4270476H1	453	706
1	405310.1.oct	4136482H1	405	718
1	405310.1.oct	036587H1	451	646
1	405310.1.oct	4536311H1	454	704
1	405310.1.oct	4268715H1	459	718
1	405310.1.oct	4792149H1	405	661
1	405310.1.oct	2477096H1	477	691
1	405310.1.oct	3359690H1	405	683
1	405310.1.oct	1944194H1	478	718
1	405310.1.oct	1944191H1	478	700
1	405310.1.oct	2475259H1	478	698
1	405310.1.oct	5684940H1	405	677
1	405310.1.oct	4853101H1	479	681
1	405310.1.oct	2479725H1	477	718
1	405310.1.oct	6385825H1	481	749
1	405310.1.oct	4979110H1	488	749
1	405310.1.oct	g1958128	406	745
1	405310.1.oct	4267935H1	491	569
1	405310.1.oct	2835323H1	494	749
1	405310.1.oct	g827193	407	554
1	405310.1.oct	4620818H1	495	773
1	405310.1.oct	5393907H1	508	780
1	405310.1.oct	3661721H1	507	772
1	405310.1.oct	3294452H1	509	756
1	405310.1.oct	524384H1	515	772
1	405310.1.oct	2136648F6	407	630
1	405310.1.oct	1297578F1	605	1008
1	405310.1.oct	2136648H1	407	655
1	405310.1.oct	1447711H1	405	638
1	405310.1.oct	1299735H1	605	837
1	405310.1.oct	1297578H1	605	832
1	405310.1.oct	3401463H1	405	647
1	405310.1.oct	1447711F6	405	889
1	405310.1.oct	2554486H1	613	840
1	405310.1.oct	3172973H1	405	638
1	405310.1.oct	g4264239	714	1177
1	405310.1.oct	5906958H1	407	697
1	405310.1.oct	5396462H1	756	1004
1	405310.1.oct	g2590966	765	1075
1	405310.1.oct	5713913H1	766	1057
1	405310.1.oct	4272548H1	786	1058
1	405310.1.oct	5399390H1	791	930
1	405310.1.oct	2856043H1	410	673
1	405310.1.oct	863574H1	804	1038
1	405310.1.oct	5056396H1	804	1078
1	405310.1.oct	4129546H2	811	1141
1	405310.1.oct	5597093H1	409	633
1	405310.1.oct	4270814H1	811	1065
1	405310.1.oct	3619064H1	813	1080
1	405310.1.oct	1506438H1	856	1060
1	405310.1.oct	4268123H1	858	1037
1	405310.1.oct	2894836H1	861	1120
1	405310.1.oct	1506438F6	865	1246
1	405310.1.oct	4272641H1	419	671
1	405310.1.oct	1424032H1	875	1115
1	405310.1.oct	5450772H1	413	646
1	405310.1.oct	2481246H1	924	1134
1	405310.1.oct	5596983H1	413	607
1	405310.1.oct	4853694H1	415	687
1	405310.1.oct	g2025894	960	1373
1	405310.1.oct	3680309H1	977	1284
1	405310.1.oct	2479705H1	1048	1287
1	405310.1.oct	4786425H1	415	546
1	405310.1.oct	2985689H1	1049	1322
1	405310.1.oct	2946253H1	417	517
1	405310.1.oct	4563856H1	417	665
1	405310.1.oct	3326068H1	1057	1335
1	405310.1.oct	4899592H1	1059	1211
1	405310.1.oct	3595144H1	419	698
1	405310.1.oct	1793730R6	1064	1511
1	405310.1.oct	2480410H1	420	636
1	405310.1.oct	1793730H1	1064	1352
1	405310.1.oct	4005512H1	1064	1352
1	405310.1.oct	3593659H1	1065	1381
1	405310.1.oct	3136794H1	422	693
1	405310.1.oct	4549670H1	1090	1203
1	405310.1.oct	730124H1	1093	1320
1	405310.1.oct	420650H1	422	694
1	405310.1.oct	841493H1	1144	1338
1	405310.1.oct	1428150H1	1148	1385
1	405310.1.oct	4704846H1	423	584
1	405310.1.oct	5850619H1	1178	1435
1	405310.1.oct	1209815R1	1198	1654
1	405310.1.oct	1209815H1	1198	1437
1	405310.1.oct	2547589H2	423	680
1	405310.1.oct	3295109H1	1199	1450
1	405310.1.oct	2452004F6	1208	1474
1	405310.1.oct	267034H1	427	771
1	405310.1.oct	6381865H1	427	712
1	405310.1.oct	g2028035	431	717
1	405310.1.oct	2452004H1	1208	1389
1	405310.1.oct	708404H1	1214	1469
1	405310.1.oct	4661117H1	1212	1468
1	405310.1.oct	705729H1	1214	1492
1	405310.1.oct	4825369H1	1228	1494
1	405310.1.oct	3162430H1	1228	1494
1	405310.1.oct	4839764H2	435	527
1	405310.1.oct	g2009002	436	749
1	405310.1.oct	4661505H1	1251	1406
1	405310.1.oct	4082148H1	1254	1528
1	405310.1.oct	150983H1	1286	1470
1	405310.1.oct	4120301H1	1296	1563
1	405310.1.oct	3749156H1	1312	1534
1	405310.1.oct	2744148H1	1323	1565
1	405310.1.oct	3137803H1	1324	1615
1	405310.1.oct	1352316T6	1366	1654
1	405310.1.oct	5218866H1	1364	1613
1	405310.1.oct	2478116H1	1379	1613
1	405310.1.oct	4375135H1	1397	1679
1	405310.1.oct	3138370H1	1417	1671
1	405310.1.oct	2797645H1	1437	1682
1	405310.1.oct	4273096H1	1466	1654
1	405310.1.oct	2136648T6	1488	1654
1	405310.1.oct	2180731F6	1494	1654
1	405310.1.oct	2180731H1	1494	1654
1	405310.1.oct	g1748137	1499	1654
1	405310.1.oct	3706106H1	1502	1668
1	405310.1.oct	5507254H1	1524	1683
1	405310.1.oct	5086666H1	1531	1754
2	480731.6.oct	4094569H1	408	558
2	480731.6.oct	4643563H1	1	254
2	480731.6.oct	4510511H1	3	242
2	480731.6.oct	3452658H1	17	192
2	480731.6.oct	1251446F1	26	623
2	480731.6.oct	2515178H1	38	333
2	480731.6.oct	2215784H1	52	272
2	480731.6.oct	4841602H1	56	299
2	480731.6.oct	g1961426	56	344
2	480731.6.oct	4571077H1	57	305
2	480731.6.oct	5216391H1	67	304
2	480731.6.oct	6137527H1	115	405

Table 4

2	480731.6.oct	1857910H1	189	464	4	237330.8.dec	2267343H1	167	411
2	480731.6.oct	1615885H1	189	390	4	237330.8.dec	2264570H1	167	419
2	480731.6.oct	086869H1	221	522	4	237330.8.dec	1349494H1	167	400
2	480731.6.oct	833867H1	237	534	4	237330.8.dec	492130H1	167	391
2	480731.6.oct	1653119H1	239	467	4	237330.8.dec	3235447H1	168	414
2	480731.6.oct	4123871H1	246	356	4	237330.8.dec	4710462H1	169	431
2	480731.6.oct	2627432H1	251	478	4	237330.8.dec	2513527H1	174	509
2	480731.6.oct	2687760H1	260	534	4	237330.8.dec	1569995H1	172	379
2	480731.6.oct	1902726H1	267	528	4	237330.8.dec	1572713H1	173	384
2	480731.6.oct	687003H1	274	493	4	237330.8.dec	3314911H1	177	416
2	480731.6.oct	878552H1	303	530	4	237330.8.dec	929441R1	178	743
2	480731.6.oct	g3280822	332	742	4	237330.8.dec	5925219H1	178	482
3	334751.2.dec	5853587H1	1	230	4	237330.8.dec	5020460H1	178	432
3	334751.2.dec	5731183H1	1	252	4	237330.8.dec	2508605F6	180	617
3	334751.2.dec	5523486H1	4	256	4	237330.8.dec	4987563H1	180	480
3	334751.2.dec	5926513H1	4	309	4	237330.8.dec	929575H1	178	415
3	334751.2.dec	2984592H1	11	268	4	237330.8.dec	3460237H1	179	414
3	334751.2.dec	g262475	107	1435	4	237330.8.dec	4836356H1	181	446
3	334751.2.dec	5732475H1	212	278	4	237330.8.dec	5894639H1	179	431
3	334751.2.dec	2667745F6	216	510	4	237330.8.dec	5897417H1	179	264
3	334751.2.dec	2667745H1	216	447	4	237330.8.dec	6382184H1	180	427
3	334751.2.dec	4418353H1	335	570	4	237330.8.dec	2508605H1	180	426
3	334751.2.dec	4882526H1	385	678	4	237330.8.dec	3417412H1	180	421
3	334751.2.dec	5612571H1	516	774	4	237330.8.dec	3373931H1	182	407
3	334751.2.dec	g2240470	551	906	4	237330.8.dec	1318328H1	180	304
3	334751.2.dec	1538335H1	605	820	4	237330.8.dec	3373939H1	181	424
3	334751.2.dec	4287276H1	627	849	4	237330.8.dec	4446212H1	183	424
3	334751.2.dec	4155393H1	811	1048	4	237330.8.dec	2448266H1	183	413
3	334751.2.dec	665879R6	858	1385	4	237330.8.dec	4910938H1	180	446
3	334751.2.dec	666190R6	858	1360	4	237330.8.dec	5378511H1	186	430
3	334751.2.dec	666190H1	858	1108	4	237330.8.dec	4940385H1	189	432
3	334751.2.dec	g759142	962	1235	4	237330.8.dec	4727560H1	196	288
3	334751.2.dec	g759141	962	1228	4	237330.8.dec	763343R1	191	741
3	334751.2.dec	4218923F6	1024	1422	4	237330.8.dec	763343H1	191	372
3	334751.2.dec	4822560H1	1024	1304	4	237330.8.dec	2731076H1	193	450
3	334751.2.dec	4218923H1	1024	1305	4	237330.8.dec	g1087562	193	555
3	334751.2.dec	4218789H1	1025	1278	4	237330.8.dec	g901772	195	568
3	334751.2.dec	4608784H1	1053	1300	4	237330.8.dec	g2100307	1134	1311
3	334751.2.dec	2959829H1	1066	1289	4	237330.8.dec	g656838	1156	1327
3	334751.2.dec	4218923T6	1176	1697	4	237330.8.dec	g884572	1168	1308
3	334751.2.dec	665879T6	1180	1690	4	237330.8.dec	2149085H1	1200	1254
3	334751.2.dec	666190T6	1196	1689	4	237330.8.dec	g1230914	1205	1317
3	334751.2.dec	5273796H1	1239	1515	4	237330.8.dec	g1761688	197	545
3	334751.2.dec	4538019H1	1254	1509	4	237330.8.dec	g942887	196	545
3	334751.2.dec	g4107592	1273	1724	4	237330.8.dec	g991000	196	510
3	334751.2.dec	955598H1	1289	1518	4	237330.8.dec	3314193H1	196	445
3	334751.2.dec	g3756020	1358	1738	4	237330.8.dec	g1735949	195	317
3	334751.2.dec	g4268857	1363	1724	4	237330.8.dec	3683715H1	198	519
3	334751.2.dec	g3447131	1377	1734	4	237330.8.dec	5031235H2	200	456
3	334751.2.dec	4635851H1	1429	1687	4	237330.8.dec	5082666H1	199	301
3	334751.2.dec	g2218832	1449	1743	4	237330.8.dec	g2024669	204	495
3	334751.2.dec	g4269639	1479	1724	4	237330.8.dec	3459624H1	206	465
3	334751.2.dec	g5449529	1483	1824	4	237330.8.dec	1786353H1	209	475
3	334751.2.dec	2878294T6	1523	1697	4	237330.8.dec	g657002	211	543
3	334751.2.dec	2878294H1	1534	1738	4	237330.8.dec	3903221H1	212	485
3	334751.2.dec	g759089	1590	1800	4	237330.8.dec	3449748H1	214	453
3	334751.2.dec	g759090	1665	1800	4	237330.8.dec	6537544H1	214	313
3	334751.2.dec	5521719H1	1674	1779	4	237330.8.dec	492371H1	216	457
4	237330.8.dec	2990340H1	1	234	4	237330.8.dec	2381611H1	218	474
4	237330.8.dec	g1694307	159	548	4	237330.8.dec	1318641H1	217	468
4	237330.8.dec	g1694113	160	546	4	237330.8.dec	g884603	224	509
4	237330.8.dec	g1509705	161	549	4	237330.8.dec	129382R1	253	749
4	237330.8.dec	5322487H1	167	394	4	237330.8.dec	129382H1	253	463
4	237330.8.dec	3376316H1	165	425	4	237330.8.dec	6128764H1	267	806
4	237330.8.dec	5480679H1	167	457	4	237330.8.dec	g2142067	266	702
4	237330.8.dec	4505409H1	167	414	4	237330.8.dec	2394231H1	291	535
4	237330.8.dec	1349494F1	167	749	4	237330.8.dec	1335369H1	327	594

Table 4

4	237330.8.dec	6384070H1	350	583
4	237330.8.dec	g1241171	366	702
4	237330.8.dec	3807596H1	368	635
4	237330.8.dec	644413H1	400	642
4	237330.8.dec	2186284H1	471	750
4	237330.8.dec	2182717H1	479	746
4	237330.8.dec	5025181H1	597	833
4	237330.8.dec	639569H1	604	858
4	237330.8.dec	3503846H1	627	786
4	237330.8.dec	2875484H1	673	939
4	237330.8.dec	6383024H1	674	982
4	237330.8.dec	6386424H1	674	955
4	237330.8.dec	3020991H1	685	899
4	237330.8.dec	3054160H1	702	1008
4	237330.8.dec	977821H1	717	926
4	237330.8.dec	977821R1	728	1277
4	237330.8.dec	5579589H1	729	990
4	237330.8.dec	5579466H1	729	975
4	237330.8.dec	1376061F1	753	1068
4	237330.8.dec	1376061H1	753	1009
4	237330.8.dec	3383765H1	753	992
4	237330.8.dec	1842579T6	765	1270
4	237330.8.dec	1842579R6	771	1151
4	237330.8.dec	1842579H1	771	1037
4	237330.8.dec	g2537725	805	1203
4	237330.8.dec	g2035761	837	1057
4	237330.8.dec	129382F1	852	1307
4	237330.8.dec	6372716H1	880	1175
4	237330.8.dec	g2670115	896	1308
4	237330.8.dec	1533561H1	904	1116
4	237330.8.dec	1732858F6	914	1308
4	237330.8.dec	4187146H1	925	1165
4	237330.8.dec	2352296H1	926	1159
4	237330.8.dec	2285290H1	932	1203
4	237330.8.dec	g1761689	937	1307
4	237330.8.dec	g1694008	947	1318
4	237330.8.dec	617499H1	973	1210
4	237330.8.dec	g1618214	972	1279
4	237330.8.dec	g1954982	978	1309
4	237330.8.dec	g2159857	989	1309
4	237330.8.dec	g1735863	989	1277
4	237330.8.dec	g4268658	991	1308
4	237330.8.dec	g1694197	995	1318
4	237330.8.dec	g1516005	996	1300
4	237330.8.dec	g3678657	997	1308
4	237330.8.dec	2273601H1	1030	1307
4	237330.8.dec	g4086537	1032	1311
4	237330.8.dec	g5540679	1036	1308
4	237330.8.dec	g3843834	1057	1308
4	237330.8.dec	478018H1	1061	1307
4	237330.8.dec	1730765H1	1084	1300
4	237330.8.dec	1732858H1	1116	1300
4	237330.8.dec	g2106685	1120	1300
5	053778.11.dec	g4190552	1810	1993
5	053778.11.dec	g5638928	1748	1991
5	053778.11.dec	2310855H1	1716	1965
5	053778.11.dec	g3785357	1716	1993
5	053778.11.dec	3289364H1	715	957
5	053778.11.dec	5693319H1	717	954
5	053778.11.dec	5603012H1	684	919
5	053778.11.dec	g2694773	1657	1993
5	053778.11.dec	g2574701	1653	1993
5	053778.11.dec	g2903963	1710	1993
5	053778.11.dec	3549629H1	1716	1961
5	053778.11.dec	5276241H1	680	909
5	053778.11.dec	3254961T6	1470	1955
5	053778.11.dec	3098021H1	1500	1799
5	053778.11.dec	g2265074	1522	1995
5	053778.11.dec	5499060H1	1521	1786
5	053778.11.dec	2371063T6	1553	1953
5	053778.11.dec	233933F1	1568	1991
5	053778.11.dec	g2350599	1569	1987
5	053778.11.dec	g1267430	1574	1987
5	053778.11.dec	1346284T6	1575	1942
5	053778.11.dec	3992844H1	1591	1835
5	053778.11.dec	3992844T6	1591	1965
5	053778.11.dec	3992844R6	1591	1986
5	053778.11.dec	g2898212	1603	1992
5	053778.11.dec	g1874440	1642	2005
5	053778.11.dec	5290716H1	1416	1666
5	053778.11.dec	2603745T6	1428	1964
5	053778.11.dec	g3146614	1427	1806
5	053778.11.dec	2110970T6	1454	1956
5	053778.11.dec	3254961R6	62	612
5	053778.11.dec	g1897652	1	173
5	053778.11.dec	4220161H1	29	330
5	053778.11.dec	g4536327	1716	1991
5	053778.11.dec	g836512	1721	1987
5	053778.11.dec	5744941H1	1231	1543
5	053778.11.dec	5490135H1	1372	1478
5	053778.11.dec	3992831H1	1231	1531
5	053778.11.dec	4535093T1	1414	1956
5	053778.11.dec	818859H1	941	1117
5	053778.11.dec	5396767T1	1126	1573
5	053778.11.dec	4800742H1	1207	1468
5	053778.11.dec	5734965H1	1092	1345
5	053778.11.dec	4111667H1	1101	1374
5	053778.11.dec	2371063H1	1463	1711
5	053778.11.dec	731630H1	1464	1720
5	053778.11.dec	2371063F6	1463	1965
5	053778.11.dec	3254961H1	62	319
5	053778.11.dec	088182H1	340	587
5	053778.11.dec	4824479H1	414	593
5	053778.11.dec	4289569H1	536	797
5	053778.11.dec	g1791805	591	772
5	053778.11.dec	3484191H1	638	913
5	053778.11.dec	4996602H1	991	1219
5	053778.11.dec	4173566H1	1017	1296
5	053778.11.dec	g760965	1029	1094
5	053778.11.dec	g2568941	1069	1494
5	053778.11.dec	2603745H1	1071	1312
5	053778.11.dec	2603745F6	1071	1448
5	053778.11.dec	g1218133	940	1251
5	053778.11.dec	1346284F6	867	1355
5	053778.11.dec	1346284H1	867	1104
5	053778.11.dec	4535093H1	843	972
6	360645.10.dec	5554128H1	1294	1562
6	360645.10.dec	3852884H1	1303	1581
6	360645.10.dec	5161636H1	1398	1666
6	360645.10.dec	1507670F6	1432	1901
6	360645.10.dec	1507670H1	1432	1635
6	360645.10.dec	1532088T6	1447	1851
6	360645.10.dec	1655614H1	1454	1583
6	360645.10.dec	4548374H1	1498	1642
6	360645.10.dec	3246721H1	68	328
6	360645.10.dec	6477162H1	70	637
6	360645.10.dec	1532088H1	107	295
6	360645.10.dec	5016056H1	115	337
6	360645.10.dec	g3932189	136	551
6	360645.10.dec	4862779H1	141	422
6	360645.10.dec	6256968H1	168	275
6	360645.10.dec	4988340H1	236	509
6	360645.10.dec	1532088F6	107	494
6	360645.10.dec	g4307092	100	555

Table 4

6	360645.10.dec	750638H1	236	457
6	360645.10.dec	4141768H1	382	652
6	360645.10.dec	3292408H1	455	707
6	360645.10.dec	3316570H1	478	740
6	360645.10.dec	4779693H1	1	100
6	360645.10.dec	492034H1	1	111
6	360645.10.dec	3433917H1	1	242
6	360645.10.dec	6389468H1	7	308
6	360645.10.dec	3943544H1	1923	2190
6	360645.10.dec	5622513H1	1793	2055
6	360645.10.dec	g813345	1181	1448
6	360645.10.dec	2185958F6	1183	1645
6	360645.10.dec	2185958H1	1183	1461
6	360645.10.dec	5471220H1	1255	1455
6	360645.10.dec	4907477H1	1269	1500
6	360645.10.dec	4931374H1	1278	1552
6	360645.10.dec	853610H1	1000	1253
6	360645.10.dec	858390H1	1000	1215
6	360645.10.dec	4118032H1	1002	1180
6	360645.10.dec	3484111H1	1003	1316
6	360645.10.dec	3749318H1	1080	1381
6	360645.10.dec	3870739H1	921	1195
6	360645.10.dec	2069602H1	713	997
6	360645.10.dec	4595933H1	866	1109
6	360645.10.dec	g1989917	889	1109
6	360645.10.dec	2741388H1	912	1038
6	360645.10.dec	g793668	929	1212
6	360645.10.dec	4328833H1	942	1196
6	360645.10.dec	5730961H1	950	1223
6	360645.10.dec	g928494	961	1126
6	360645.10.dec	3945858H1	980	1249
6	360645.10.dec	2757979H1	992	1268
6	360645.10.dec	2607858F6	29	368
6	360645.10.dec	2607858H1	29	285
6	360645.10.dec	3346552H1	33	145
6	360645.10.dec	3286166H2	33	136
6	360645.10.dec	3111874H1	33	167
6	360645.10.dec	3392281H1	40	317
6	360645.10.dec	4003719H1	58	110
6	360645.10.dec	2419778H1	622	849
6	360645.10.dec	2069602F6	713	1121
7	334808.1.dec	1630022F6	1019	1491
7	334808.1.dec	4173650H1	1060	1351
7	334808.1.dec	6497920H1	1131	1695
7	334808.1.dec	1501183H1	1170	1360
7	334808.1.dec	5946616H1	1175	1444
7	334808.1.dec	3536430H1	1280	1583
7	334808.1.dec	6113586H1	1334	1506
7	334808.1.dec	g5178927	1484	1869
7	334808.1.dec	2240592H1	58	266
7	334808.1.dec	4053310H1	644	809
7	334808.1.dec	2182165H1	815	1074
7	334808.1.dec	4517464H1	847	1058
7	334808.1.dec	5068320H1	936	1209
7	334808.1.dec	1630016H1	1019	1217
7	334808.1.dec	g3849718	1493	1865
7	334808.1.dec	1633870F6	1561	1862
7	334808.1.dec	1633870H1	1561	1768
7	334808.1.dec	g2789460	1	1855
7	334808.1.dec	4671034H1	48	319
7	334808.1.dec	2240592F6	58	398
8	997089.7.dec	2728454H1	1266	1518
8	997089.7.dec	3325820H1	1266	1537
8	997089.7.dec	1619209H1	1266	1476
8	997089.7.dec	4398554H1	1268	1523
8	997089.7.dec	3772613H1	1286	1547
8	997089.7.dec	4336363H1	1094	1366
8	997089.7.dec	1576186F6	1098	1373
8	997089.7.dec	1576186H1	1098	1322
8	997089.7.dec	2538386H1	1098	1351
8	997089.7.dec	4822363H1	1106	1367
8	997089.7.dec	3485650H1	915	1162
8	997089.7.dec	1786234H1	945	1188
8	997089.7.dec	5593308H1	948	1203
8	997089.7.dec	g1976837	820	1136
8	997089.7.dec	6406736H1	830	1298
8	997089.7.dec	4063260H1	863	1028
8	997089.7.dec	4539449H1	861	1139
8	997089.7.dec	809033H1	868	940
8	997089.7.dec	3699229H1	873	1171
8	997089.7.dec	g1556965	876	1186
8	997089.7.dec	4691278H1	878	1129
8	997089.7.dec	1426405H1	886	1085
8	997089.7.dec	4847630H1	887	1152
8	997089.7.dec	3467813H1	896	1135
8	997089.7.dec	g2020678	1019	1284
8	997089.7.dec	3819954H1	1018	1297
8	997089.7.dec	2104288H1	1024	1112
8	997089.7.dec	2808341H1	1025	1307
8	997089.7.dec	4066658H1	1032	1289
8	997089.7.dec	5309516H1	1052	1306
8	997089.7.dec	5592153H1	1118	1392
8	997089.7.dec	4978966H1	1134	1414
8	997089.7.dec	g616650	1141	1418
8	997089.7.dec	4912405H1	1152	1438
8	997089.7.dec	4337708H1	1152	1442
8	997089.7.dec	3940620H1	1154	1425
8	997089.7.dec	g2003478	1156	1533
8	997089.7.dec	755318H1	1161	1374
8	997089.7.dec	1252324H1	1242	1469
8	997089.7.dec	5435704H1	1242	1496
8	997089.7.dec	4539673H1	1263	1493
8	997089.7.dec	5331905H1	1231	1475
8	997089.7.dec	5052492H1	1236	1463
8	997089.7.dec	g389176	1238	1467
8	997089.7.dec	1872382F6	951	1432
8	997089.7.dec	1872382H1	951	1216
8	997089.7.dec	g2001948	956	1341
8	997089.7.dec	g2785527	961	1184
8	997089.7.dec	g2785350	967	1045
8	997089.7.dec	3416911H1	972	1221
8	997089.7.dec	1692077H1	982	1064
8	997089.7.dec	3586654H1	992	1315
8	997089.7.dec	4256810H1	995	1275
8	997089.7.dec	g1970619	1003	1276
8	997089.7.dec	2742103H1	1006	1256
8	997089.7.dec	701814H1	1496	1731
8	997089.7.dec	4336416H1	1486	1774
8	997089.7.dec	2624908H1	1491	1713
8	997089.7.dec	1849263H1	1491	1584
8	997089.7.dec	g573048	1498	1856
8	997089.7.dec	1613441H1	1498	1705
8	997089.7.dec	g672219	1498	1845
8	997089.7.dec	1809483H1	1498	1755
8	997089.7.dec	3943866H1	753	1015
8	997089.7.dec	g3889303	753	958
8	997089.7.dec	5995872H1	762	1049
8	997089.7.dec	723432R1	764	1342
8	997089.7.dec	723432H1	764	955
8	997089.7.dec	3332343H1	769	1019
8	997089.7.dec	1960570H1	775	1062
8	997089.7.dec	6482560H1	782	1326
8	997089.7.dec	598929H1	785	899
8	997089.7.dec	2558439H1	1222	1473

Table 4

8	997089.7.dec	1575796H1	1222	1399
8	997089.7.dec	3109970H1	1224	1502
8	997089.7.dec	5732514H1	1223	1506
8	997089.7.dec	927100H1	1232	1493
8	997089.7.dec	1731008H1	1504	1734
8	997089.7.dec	g1740574	1510	1685
8	997089.7.dec	5527051H1	1524	1766
8	997089.7.dec	6398114H1	1523	1751
8	997089.7.dec	4126433H1	1524	1793
8	997089.7.dec	5186537H1	1529	1706
8	997089.7.dec	5432074H1	1532	1779
8	997089.7.dec	3942839H1	1537	1810
8	997089.7.dec	4439832H1	812	1020
8	997089.7.dec	3570124H1	813	1111
8	997089.7.dec	3330642H1	813	1081
8	997089.7.dec	4332312H1	576	838
8	997089.7.dec	6521581H1	616	988
8	997089.7.dec	5656215H1	639	901
8	997089.7.dec	3336136H1	652	895
8	997089.7.dec	1428142F6	669	1144
8	997089.7.dec	1428142H1	669	919
8	997089.7.dec	g389543	708	1100
8	997089.7.dec	3668538H1	713	997
8	997089.7.dec	5042704H1	714	949
8	997089.7.dec	3699552H1	717	999
8	997089.7.dec	5156683H1	51	295
8	997089.7.dec	g2020020	84	533
8	997089.7.dec	6302085H1	228	530
8	997089.7.dec	4444078H1	288	515
8	997089.7.dec	5623338H1	507	827
8	997089.7.dec	4329118H1	576	821
8	997089.7.dec	g698738	1498	1841
8	997089.7.dec	g698716	1499	1824
8	997089.7.dec	3796755H1	1391	1705
8	997089.7.dec	3772065H1	1393	1683
8	997089.7.dec	2921912H1	1400	1679
8	997089.7.dec	1338386H1	1406	1640
8	997089.7.dec	2208068H1	1792	1876
8	997089.7.dec	2909601H1	1797	1876
8	997089.7.dec	2415770H1	1800	1855
8	997089.7.dec	3857026H1	1801	1868
8	997089.7.dec	2455789H1	5	224
8	997089.7.dec	6602471H1	5	143
8	997089.7.dec	924429H1	1	170
8	997089.7.dec	6477763H1	1	564
8	997089.7.dec	3687663H1	9	307
8	997089.7.dec	4423309H1	22	307
8	997089.7.dec	5044370H1	22	287
8	997089.7.dec	3834620H1	23	302
8	997089.7.dec	659525H1	1363	1640
8	997089.7.dec	5527891H1	1364	1473
8	997089.7.dec	2532712H1	1377	1691
8	997089.7.dec	4321548H1	1379	1653
8	997089.7.dec	1427885H1	1437	1675
8	997089.7.dec	4063504H1	1443	1706
8	997089.7.dec	2326755H1	1447	1685
8	997089.7.dec	1793547H1	1454	1753
8	997089.7.dec	755323R1	1462	1850
8	997089.7.dec	755323H1	1462	1675
8	997089.7.dec	3942852H1	1538	1809
8	997089.7.dec	3943170H1	1538	1803
8	997089.7.dec	4823018H1	1541	1686
8	997089.7.dec	6166630H1	1562	1850
8	997089.7.dec	4049271H1	1351	1534
8	997089.7.dec	3674696H1	1357	1479
8	997089.7.dec	4144117H1	1464	1752
8	997089.7.dec	5733971H1	1470	1729
8	997089.7.dec	899613H1	1483	1735
8	997089.7.dec	755318R1	1161	1689
8	997089.7.dec	g825993	1172	1536
8	997089.7.dec	3821487H1	1174	1287
8	997089.7.dec	3293579H1	1182	1416
8	997089.7.dec	3441662H1	1183	1410
8	997089.7.dec	1239073H1	1191	1432
8	997089.7.dec	g3840776	1413	1762
8	997089.7.dec	4871671H1	1433	1701
8	997089.7.dec	2253321H1	1808	1876
8	997089.7.dec	1794040H1	1808	1876
8	997089.7.dec	g2018816	1823	1876
8	997089.7.dec	g685621	717	1020
8	997089.7.dec	2700859H1	723	995
8	997089.7.dec	3513894H1	749	990
8	997089.7.dec	292713H1	1293	1557
8	997089.7.dec	1864784H1	1302	1566
8	997089.7.dec	g942975	1310	1616
8	997089.7.dec	2360739H1	1326	1567
8	997089.7.dec	5731187H1	1335	1589
8	997089.7.dec	1733703H1	1336	1552
8	997089.7.dec	5690180H1	1339	1529
8	997089.7.dec	1863109H1	1702	1850
8	997089.7.dec	2102105H1	1694	1850
8	997089.7.dec	4339688H1	1703	1850
8	997089.7.dec	3817576H1	1694	1850
8	997089.7.dec	5353591H1	1736	1850
8	997089.7.dec	3798035H1	1736	1850
8	997089.7.dec	4399365H1	1737	1850
8	997089.7.dec	4521845H1	1737	1850
8	997089.7.dec	1629818H1	1748	1850
8	997089.7.dec	6480664H1	1678	1879
8	997089.7.dec	3055643H1	1674	1850
8	997089.7.dec	707490H1	1680	1849
8	997089.7.dec	1945259H1	1682	1863
8	997089.7.dec	3127913H1	1682	1850
8	997089.7.dec	1483348H1	1682	1850
8	997089.7.dec	554627H1	1686	1850
8	997089.7.dec	704029H1	1686	1782
8	997089.7.dec	1004810H1	1625	1834
8	997089.7.dec	g616388	1637	1850
8	997089.7.dec	982190H1	1652	1850
8	997089.7.dec	3803295H1	1652	1782
8	997089.7.dec	3750923H1	1656	1850
8	997089.7.dec	1533117H1	1586	1800
8	997089.7.dec	5042002H1	1597	1845
8	997089.7.dec	2103420H1	1601	1729
8	997089.7.dec	1628004H1	1585	1791
8	997089.7.dec	761529H1	1610	1849
8	997089.7.dec	4212159H1	1612	1859
8	997089.7.dec	3846656H1	1623	1850
8	997089.7.dec	5546414H1	1194	1388
8	997089.7.dec	4073632H1	1202	1491
8	997089.7.dec	1703681H1	1209	1394
8	997089.7.dec	4441637H1	1212	1407
8	997089.7.dec	g1988696	1214	1646
8	997089.7.dec	5677789H1	1216	1461
8	997089.7.dec	2019819H1	1216	1396
8	997089.7.dec	4515993H1	1341	1551
8	997089.7.dec	4420186H1	1348	1596
8	997089.7.dec	1995894H1	1349	1588
8	997089.7.dec	5338351H1	1562	1810
8	997089.7.dec	g1716174	1562	1721
8	997089.7.dec	6166622H1	1562	1876
8	997089.7.dec	1483801H1	1562	1842
8	997089.7.dec	1294123H1	1567	1796
8	997089.7.dec	4770575H1	1570	1845

Table 4

8	997089.7.dec	6484611H1	1572	1879
8	997089.7.dec	1985045R6	1577	1876
8	997089.7.dec	1985088H1	1578	1829
8	997089.7.dec	2863664H1	1578	1883
8	997089.7.dec	3295858H1	1584	1811
8	997089.7.dec	5320722H1	1757	1851
8	997089.7.dec	5481892H1	1757	1850
8	997089.7.dec	4644039H1	1756	1850
8	997089.7.dec	1450379F6	1767	1863
8	997089.7.dec	5575661H1	1767	1855
8	997089.7.dec	1450379H1	1767	1850
8	997089.7.dec	1406936H1	1767	1850
8	997089.7.dec	3841989H1	1770	1850
8	997089.7.dec	857233H1	1781	1876
8	997089.7.dec	1384904H1	1784	1850
8	997089.7.dec	1384944H1	1784	1855
8	997089.7.dec	6299830H1	1787	1876
9	237152.1.dec	g3687842	1	1044
9	237152.1.dec	g3355903	68	691
9	237152.1.dec	313182R6	185	705
9	237152.1.dec	313182H1	185	370
9	237152.1.dec	g5663312	396	527
9	237152.1.dec	313182T6	433	911
9	237152.1.dec	g3677047	558	1006
9	237152.1.dec	g3931239	566	928
9	237152.1.dec	g5111586	593	1047
9	237152.1.dec	g4070077	593	1028
9	237152.1.dec	g4630148	593	1019
9	237152.1.dec	g4891722	593	994
9	237152.1.dec	g3202771	593	986
9	237152.1.dec	g3744753	593	991
9	237152.1.dec	g1487039	593	982
9	237152.1.dec	g1225112	593	981
9	237152.1.dec	g1268065	593	808
9	237152.1.dec	g1272058	673	1040
9	237152.1.dec	g1858070	742	1045
9	237152.1.dec	g1487086	780	1035
9	237152.1.dec	g1302749	819	1039
9	237152.1.dec	1814203F6	820	1241
9	237152.1.dec	1814199H1	820	1018
9	237152.1.dec	894609H1	821	1068
9	237152.1.dec	g3322196	885	1037
9	237152.1.dec	3802778H1	1003	1109
9	237152.1.dec	g5364335	1062	1505
9	237152.1.dec	6379454H1	1067	1333
9	237152.1.dec	g3835124	1075	1514
9	237152.1.dec	g4899943	1095	1513
9	237152.1.dec	g1856934	1098	1513
9	237152.1.dec	g3931985	1107	1514
9	237152.1.dec	g3933174	1291	1517
10	232851.7.dec	1971311F6	361	824
10	232851.7.dec	4377213H1	632	869
10	232851.7.dec	4372757H1	698	989
10	232851.7.dec	1971311H1	361	605
10	232851.7.dec	3236558H2	382	578
10	232851.7.dec	3646182H1	386	668
10	232851.7.dec	g1633875	391	657
10	232851.7.dec	3743671H1	896	1207
10	232851.7.dec	g2106789	443	676
10	232851.7.dec	4363458H1	491	574
10	232851.7.dec	4589686H1	525	784
10	232851.7.dec	1514410H6	570	776
10	232851.7.dec	1514410F6	570	973
10	232851.7.dec	g2080694	62	176
10	232851.7.dec	2560491H1	82	341
10	232851.7.dec	431388H1	87	310
10	232851.7.dec	4634517H1	114	409
10	232851.7.dec	4854011H1	236	489
10	232851.7.dec	4898831H1	58	346
10	232851.7.dec	4590044H1	939	1209
10	232851.7.dec	g990847	1044	1426
10	232851.7.dec	2633312F6	1061	1604
10	232851.7.dec	2633312H1	1061	1248
10	232851.7.dec	3880543H1	1200	1470
10	232851.7.dec	5001383H1	1197	1459
10	232851.7.dec	3089512H1	1374	1658
10	232851.7.dec	2950963H1	1379	1667
10	232851.7.dec	2269908H1	1492	1738
10	232851.7.dec	5874154H1	1394	1671
10	232851.7.dec	875919R1	1397	1815
10	232851.7.dec	875919H1	1397	1626
10	232851.7.dec	134999H1	1410	1569
10	232851.7.dec	3165201H1	1430	1694
10	232851.7.dec	2211323H1	1440	1673
10	232851.7.dec	6516735H1	1440	1803
10	232851.7.dec	3180284H1	1460	1750
10	232851.7.dec	5528389H1	1474	1627
10	232851.7.dec	2749071H1	1505	1764
10	232851.7.dec	4447784H1	1508	1768
10	232851.7.dec	g2740439	1593	2002
10	232851.7.dec	1914536H1	1	275
10	232851.7.dec	2193227F6	43	420
10	232851.7.dec	2193227H1	43	291
11	083804.1.dec	g2231165	1	1807
11	083804.1.dec	g2245579	1	180
11	083804.1.dec	g1468978	38	2382
11	083804.1.dec	2505102H1	48	281
11	083804.1.dec	g2626807	50	1475
11	083804.1.dec	g3764994	1553	1910
11	083804.1.dec	2139585H1	1835	2094
11	083804.1.dec	4670914H1	1931	2177
12	272721.6.oct	3440665H2	2422	2746
12	272721.6.oct	1879622T6	2423	2899
12	272721.6.oct	4697847H1	2424	2686
12	272721.6.oct	6365882H1	2436	2760
12	272721.6.oct	g2717112	2439	2941
12	272721.6.oct	6156113H1	2446	2767
12	272721.6.oct	1614372H1	2447	2659
12	272721.6.oct	2669613H1	2450	2701
12	272721.6.oct	2992666H1	2452	2747
12	272721.6.oct	3606557H1	2457	2747
12	272721.6.oct	2383864T6	2461	2889
12	272721.6.oct	g2017289	2464	2763
12	272721.6.oct	4771302H1	2464	2731
12	272721.6.oct	1626533H1	2470	2679
12	272721.6.oct	2081464H1	2475	2746
12	272721.6.oct	1443934R1	2646	2946
12	272721.6.oct	g847460	2646	2941
12	272721.6.oct	g3191774	2646	2946
12	272721.6.oct	g1670679	2647	2951
12	272721.6.oct	818394H1	2651	2930
12	272721.6.oct	g2958359	2658	2939
12	272721.6.oct	g2197785	2659	2941
12	272721.6.oct	207900H1	2668	2917
12	272721.6.oct	g1664674	2679	2945
12	272721.6.oct	g2218503	2680	2930
12	272721.6.oct	g765746	2686	2948
12	272721.6.oct	4632778H1	2687	2928
12	272721.6.oct	853091T1	2693	2877
12	272721.6.oct	g4330145	2694	2943
12	272721.6.oct	853091H1	2704	2919
12	272721.6.oct	858358H1	2704	2919
12	272721.6.oct	1738239H1	2716	2934
12	272721.6.oct	255380H1	2722	2944

Table 4

12	272721.6.oct	4174516H1	2721	2919
12	272721.6.oct	2909246H1	2722	2919
12	272721.6.oct	255435H1	2722	2795
12	272721.6.oct	g1154004	2732	2939
12	272721.6.oct	g3922704	2733	2937
12	272721.6.oct	g4196202	2735	2940
12	272721.6.oct	g4306565	2736	2942
12	272721.6.oct	g4535419	2737	2941
12	272721.6.oct	g3743992	2738	2941
12	272721.6.oct	g2704053	2757	2941
12	272721.6.oct	4504538H1	2765	2941
12	272721.6.oct	206466H1	2768	2941
12	272721.6.oct	4517424H1	2775	2955
12	272721.6.oct	g1733236	2783	2941
12	272721.6.oct	2318583H1	2783	2949
12	272721.6.oct	5528408H1	2787	2941
12	272721.6.oct	4983352H1	2801	2930
12	272721.6.oct	1624794H1	2801	3003
12	272721.6.oct	4637844H1	2809	2946
12	272721.6.oct	4590517H1	2855	2944
12	272721.6.oct	899136T1	2861	2912
12	272721.6.oct	899136H1	2861	2949
12	272721.6.oct	899136R1	2861	2949
12	272721.6.oct	5117025H1	2023	2284
12	272721.6.oct	5683880H1	2025	2255
12	272721.6.oct	3359193H1	2025	2207
12	272721.6.oct	4198026H1	2025	2311
12	272721.6.oct	3140673H1	2027	2304
12	272721.6.oct	5189358H1	2032	2272
12	272721.6.oct	5714512H1	2032	2319
12	272721.6.oct	309502H1	2034	2267
12	272721.6.oct	1532541H1	2038	2254
12	272721.6.oct	4321903H1	2041	2311
12	272721.6.oct	g1717680	2043	2346
12	272721.6.oct	g1956033	2046	2359
12	272721.6.oct	4544903H1	2048	2306
12	272721.6.oct	g2030407	2048	2470
12	272721.6.oct	4649950H1	2048	2289
12	272721.6.oct	1688977H1	2048	2276
12	272721.6.oct	485575H1	2052	2276
12	272721.6.oct	3806025H1	2055	2357
12	272721.6.oct	336429H1	2057	2308
12	272721.6.oct	886448H1	2058	2304
12	272721.6.oct	5984480H1	11	195
12	272721.6.oct	4177301H1	16	278
12	272721.6.oct	2632475H1	17	266
12	272721.6.oct	5043035H1	19	269
12	272721.6.oct	3373560H1	19	284
12	272721.6.oct	2852069H1	22	240
12	272721.6.oct	4837381H1	22	276
12	272721.6.oct	654603H1	22	275
12	272721.6.oct	4836245H1	22	263
12	272721.6.oct	5082455H1	22	205
12	272721.6.oct	6101447H1	24	302
12	272721.6.oct	3697626H1	28	302
12	272721.6.oct	3747069H1	29	321
12	272721.6.oct	1389988H1	46	269
12	272721.6.oct	4672018H1	48	213
12	272721.6.oct	g2111559	142	587
12	272721.6.oct	4558830H1	144	270
12	272721.6.oct	4739703H1	170	396
12	272721.6.oct	3349536H1	176	446
12	272721.6.oct	2883139F6	226	616
12	272721.6.oct	1818319H1	317	570
12	272721.6.oct	5500902H1	426	567
12	272721.6.oct	5500602H1	427	661
12	272721.6.oct	2383864F6	427	876
12	272721.6.oct	4881036H1	440	671
12	272721.6.oct	5614719H1	540	818
12	272721.6.oct	5197812H2	542	761
12	272721.6.oct	3556769H1	544	734
12	272721.6.oct	861316H1	570	801
12	272721.6.oct	5158893H2	574	753
12	272721.6.oct	1336222H1	589	836
12	272721.6.oct	1337943F6	589	840
12	272721.6.oct	1337943H1	589	823
12	272721.6.oct	1335885H1	589	818
12	272721.6.oct	2549642H1	3	223
12	272721.6.oct	3421029H1	1	252
12	272721.6.oct	3462469H1	4	262
12	272721.6.oct	3530456H1	7	311
12	272721.6.oct	5494835H1	11	253
12	272721.6.oct	2103317H1	9	246
12	272721.6.oct	4251547H1	10	227
12	272721.6.oct	1880511H1	2058	2316
12	272721.6.oct	2608041H1	2058	2296
12	272721.6.oct	886448R1	2058	2601
12	272721.6.oct	g847286	2062	2263
12	272721.6.oct	g847459	2063	2406
12	272721.6.oct	4858132H1	2064	2320
12	272721.6.oct	5922776H1	2066	2330
12	272721.6.oct	3172609H1	2069	2342
12	272721.6.oct	4093703H1	2068	2341
12	272721.6.oct	3380145H1	2072	2263
12	272721.6.oct	g1187212	2074	2478
12	272721.6.oct	4514781H1	2078	2344
12	272721.6.oct	1812403H1	2083	2312
12	272721.6.oct	3631939H1	2085	2343
12	272721.6.oct	310785H1	2085	2257
12	272721.6.oct	4876369H1	2091	2288
12	272721.6.oct	2796749H1	2091	2374
12	272721.6.oct	5041972H1	2096	2320
12	272721.6.oct	620219H1	2097	2368
12	272721.6.oct	4761379H1	2102	2368
12	272721.6.oct	5086430H1	2105	2237
12	272721.6.oct	4195205H1	2116	2394
12	272721.6.oct	2824550H1	2118	2444
12	272721.6.oct	5887053H1	2129	2382
12	272721.6.oct	5568231H1	2126	2382
12	272721.6.oct	1419784H1	2126	2359
12	272721.6.oct	1701231H1	2127	2345
12	272721.6.oct	850902R1	2129	2726
12	272721.6.oct	5890366H1	2129	2258
12	272721.6.oct	850902H1	2129	2357
12	272721.6.oct	964020H1	2129	2391
12	272721.6.oct	5883243H1	2131	2441
12	272721.6.oct	1979478R6	2133	2621
12	272721.6.oct	623173H1	2134	2388
12	272721.6.oct	4304636H1	2133	2348
12	272721.6.oct	4304619H1	2133	2355
12	272721.6.oct	1211746H1	2137	2376
12	272721.6.oct	1211746R1	2137	2584
12	272721.6.oct	544305H1	2140	2289
12	272721.6.oct	959104H1	2147	2306
12	272721.6.oct	2737633H1	2157	2397
12	272721.6.oct	4243666H1	2168	2424
12	272721.6.oct	1784361H1	2168	2452
12	272721.6.oct	689468H1	2173	2423
12	272721.6.oct	5618378H1	2175	2375
12	272721.6.oct	2707953H1	2181	2481
12	272721.6.oct	4182894H1	2180	2428
12	272721.6.oct	1808379H1	2191	2400
12	272721.6.oct	3648072H1	2192	2491
12	272721.6.oct	g2069859	2190	2624

Table 4

12	272721.6.oct	3651272H1	2193	2488
12	272721.6.oct	544858H1	2193	2427
12	272721.6.oct	359974H1	2193	2423
12	272721.6.oct	806833H1	2197	2447
12	272721.6.oct	1800635H1	2198	2387
12	272721.6.oct	4126223H1	2198	2279
12	272721.6.oct	409008H1	2199	2379
12	272721.6.oct	4630512H1	2206	2469
12	272721.6.oct	4121202H1	2227	2497
12	272721.6.oct	5953089H1	1986	2269
12	272721.6.oct	5952929H1	1986	2296
12	272721.6.oct	4507393H1	1993	2262
12	272721.6.oct	4301314H1	2003	2273
12	272721.6.oct	961005H1	2004	2294
12	272721.6.oct	961005R2	2004	2553
12	272721.6.oct	g2218572	2008	2176
12	272721.6.oct	1638726H1	2013	2215
12	272721.6.oct	4375107H1	2013	2293
12	272721.6.oct	1638757H1	2013	2220
12	272721.6.oct	4168120H1	2018	2294
12	272721.6.oct	5152124H1	2018	2289
12	272721.6.oct	157823H1	2018	2201
12	272721.6.oct	157823R1	2018	2293
12	272721.6.oct	3564117H1	2019	2319
12	272721.6.oct	206466F1	2020	2639
12	272721.6.oct	4646215H1	1902	2174
12	272721.6.oct	4646289H1	1902	2072
12	272721.6.oct	4855045H1	1902	2096
12	272721.6.oct	2108791H1	1903	2076
12	272721.6.oct	2584487H1	1903	2070
12	272721.6.oct	g734039	1903	2248
12	272721.6.oct	2822283H1	1904	2106
12	272721.6.oct	4508977H1	1906	2154
12	272721.6.oct	1534302H1	1913	2124
12	272721.6.oct	1531421H1	1913	2110
12	272721.6.oct	1531611H1	1913	2117
12	272721.6.oct	3560701H1	1914	2240
12	272721.6.oct	g1957940	1920	2295
12	272721.6.oct	4370273H1	1924	2150
12	272721.6.oct	4370270H1	1924	2192
12	272721.6.oct	3954918H1	1932	2195
12	272721.6.oct	3955545H1	1932	2194
12	272721.6.oct	4742017H1	1934	2070
12	272721.6.oct	2946355H1	1935	2254
12	272721.6.oct	3341847H1	1935	2166
12	272721.6.oct	3629088H1	1935	2211
12	272721.6.oct	857934H1	1937	2186
12	272721.6.oct	4218690H1	1940	2043
12	272721.6.oct	g1664571	1940	2356
12	272721.6.oct	g1792741	1940	2291
12	272721.6.oct	2255504H1	1944	2178
12	272721.6.oct	2180294H1	1955	2076
12	272721.6.oct	4442810H1	1956	2233
12	272721.6.oct	g1745686	1968	2294
12	272721.6.oct	5069083H1	1973	2246
12	272721.6.oct	4605016H1	1973	2228
12	272721.6.oct	949436H1	1973	2190
12	272721.6.oct	948233H1	1973	2221
12	272721.6.oct	1798444H1	1979	2252
12	272721.6.oct	176025H1	1981	2261
12	272721.6.oct	2203232H1	1983	2222
12	272721.6.oct	g1670678	1579	1968
12	272721.6.oct	909010H1	1578	1866
12	272721.6.oct	5390293H1	1578	1810
12	272721.6.oct	5038305H1	1582	1849
12	272721.6.oct	3975017H1	1584	1861
12	272721.6.oct	5681103H1	1593	1851
12	272721.6.oct	3511433H1	1596	1868
12	272721.6.oct	3443682H1	1633	1900
12	272721.6.oct	3554817H1	1634	1917
12	272721.6.oct	4795906H1	1635	1856
12	272721.6.oct	1689619F6	1640	1958
12	272721.6.oct	1689619H1	1640	1844
12	272721.6.oct	5425548H1	1643	1748
12	272721.6.oct	3238705H1	1644	1898
12	272721.6.oct	3766967H1	1658	1951
12	272721.6.oct	3049524H1	1663	1954
12	272721.6.oct	3566758H1	1666	1968
12	272721.6.oct	2596290H1	1672	1917
12	272721.6.oct	3160455H1	1676	1956
12	272721.6.oct	5265155H1	1690	1944
12	272721.6.oct	2073037H1	1694	1967
12	272721.6.oct	4888491H1	1696	1949
12	272721.6.oct	2796725H1	1696	1956
12	272721.6.oct	4211481H1	2341	2596
12	272721.6.oct	4547403H1	2344	2591
12	272721.6.oct	g1626091	2345	2556
12	272721.6.oct	290356T6	2354	2922
12	272721.6.oct	g1996936	2358	2621
12	272721.6.oct	387322H1	2362	2642
12	272721.6.oct	3532652H1	2368	2616
12	272721.6.oct	5787013H1	2370	2644
12	272721.6.oct	5784572H1	2370	2676
12	272721.6.oct	5789842H1	2370	2660
12	272721.6.oct	5794037H1	2370	2671
12	272721.6.oct	5788592H1	2370	2671
12	272721.6.oct	5787092H1	2370	2645
12	272721.6.oct	3408832H1	2374	2613
12	272721.6.oct	2932187H1	2378	2633
12	272721.6.oct	5465681H1	2381	2547
12	272721.6.oct	g1979728	2388	2621
12	272721.6.oct	3500620H1	2389	2671
12	272721.6.oct	1979478T6	2392	2892
12	272721.6.oct	6373060H1	2398	2647
12	272721.6.oct	206466R1	2399	2941
12	272721.6.oct	1709367H1	2408	2623
12	272721.6.oct	5137771H1	2416	2675
12	272721.6.oct	1906004H1	2419	2675
12	272721.6.oct	2419956H1	2419	2659
12	272721.6.oct	4709480H1	631	755
12	272721.6.oct	4759041H1	634	856
12	272721.6.oct	2212119H1	644	890
12	272721.6.oct	4875152H1	653	838
12	272721.6.oct	1794525H1	675	943
12	272721.6.oct	1697241H1	685	928
12	272721.6.oct	3556564H1	689	972
12	272721.6.oct	4444063H1	731	963
12	272721.6.oct	4205033H1	737	862
12	272721.6.oct	3170922H1	741	1007
12	272721.6.oct	2540429H1	771	1004
12	272721.6.oct	3209223H1	781	1065
12	272721.6.oct	4779512H1	803	948
12	272721.6.oct	5038225H1	810	884
12	272721.6.oct	4760088H1	810	881
12	272721.6.oct	4794851H1	831	1067
12	272721.6.oct	g1961401	872	1287
12	272721.6.oct	993703H1	881	1101
12	272721.6.oct	3802142H1	890	1155
12	272721.6.oct	5436252H1	892	1092
12	272721.6.oct	g1984201	898	1344
12	272721.6.oct	657267H1	944	1186
12	272721.6.oct	2531018H1	956	1178
12	272721.6.oct	3686443H1	969	1257
12	272721.6.oct	2821084H1	970	1263

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12	272721.6.oct	5391261H1	990	1130
12	272721.6.oct	860948H1	992	1237
12	272721.6.oct	4602249H1	996	1250
12	272721.6.oct	2258436H1	998	1215
12	272721.6.oct	g1979122	1002	1404
12	272721.6.oct	g2030330	1006	1373
12	272721.6.oct	3049484H1	1016	1296
12	272721.6.oct	5422806H1	1015	1277
12	272721.6.oct	4875712H1	1017	1283
12	272721.6.oct	2930958H1	1038	1321
12	272721.6.oct	939670H1	1040	1283
12	272721.6.oct	3785755H1	1047	1231
12	272721.6.oct	3552260H1	1064	1369
12	272721.6.oct	1443934H1	1069	1329
12	272721.6.oct	2119473H1	1072	1301
12	272721.6.oct	3359947H1	1086	1331
12	272721.6.oct	5205141H2	1087	1238
12	272721.6.oct	3725856H1	1127	1436
12	272721.6.oct	4543655H1	1134	1376
12	272721.6.oct	881722R1	1134	1711
12	272721.6.oct	881722H1	1134	1256
12	272721.6.oct	568864H1	1149	1408
12	272721.6.oct	2734131H1	1149	1405
12	272721.6.oct	5445609H1	1166	1365
12	272721.6.oct	4894901H1	1176	1406
12	272721.6.oct	g1860192	2578	2937
12	272721.6.oct	1940615T6	2583	2902
12	272721.6.oct	5068437H1	2579	2852
12	272721.6.oct	1940615R6	2583	2939
12	272721.6.oct	1940615H1	2583	2822
12	272721.6.oct	g4222524	2588	2936
12	272721.6.oct	4950868H1	2589	2841
12	272721.6.oct	g4110048	2590	2947
12	272721.6.oct	600791H1	2591	2836
12	272721.6.oct	4981557H1	2595	2850
12	272721.6.oct	g4452122	2596	2939
12	272721.6.oct	g1114427	2602	2930
12	272721.6.oct	g4451191	2599	2940
12	272721.6.oct	g892675	2605	2957
12	272721.6.oct	g3424444	2604	2945
12	272721.6.oct	g2111560	2604	2950
12	272721.6.oct	g1982175	2608	2946
12	272721.6.oct	g3919967	2606	2942
12	272721.6.oct	g4391891	2606	2941
12	272721.6.oct	3624992H1	2608	2896
12	272721.6.oct	g3918885	2603	2938
12	272721.6.oct	4635746H1	2612	2867
12	272721.6.oct	885047T1	2613	2896
12	272721.6.oct	885047H1	2613	2919
12	272721.6.oct	2397225H1	2613	2842
12	272721.6.oct	g2397616	2619	2934
12	272721.6.oct	g2212530	2621	2961
12	272721.6.oct	4362360H1	2629	2904
12	272721.6.oct	g1522152	2629	2861
12	272721.6.oct	386546H1	2631	2917
12	272721.6.oct	g3117517	2631	2950
12	272721.6.oct	g1157968	2632	2941
12	272721.6.oct	344052H1	2633	2821
12	272721.6.oct	2632475T6	2634	2896
12	272721.6.oct	g4114251	2636	2940
12	272721.6.oct	g4136680	2635	2949
12	272721.6.oct	g3017010	2638	2930
12	272721.6.oct	g4284054	2638	2946
12	272721.6.oct	389040H1	2645	2941
12	272721.6.oct	g4328908	2480	2951
12	272721.6.oct	2271363T6	2484	2901
12	272721.6.oct	1549356H1	2486	2610
12	272721.6.oct	g4085144	2492	2940
12	272721.6.oct	g3245239	2491	2940
12	272721.6.oct	1629148T6	2500	2899
12	272721.6.oct	3375874H1	2500	2762
12	272721.6.oct	g4107892	2506	2956
12	272721.6.oct	g3796949	2507	2930
12	272721.6.oct	g2342174	2517	2936
12	272721.6.oct	3705402H1	2518	2744
12	272721.6.oct	3665055H1	2522	2818
12	272721.6.oct	g518303	2516	2946
12	272721.6.oct	g1664375	2524	2945
12	272721.6.oct	g4531573	2531	2946
12	272721.6.oct	415664H1	2535	2761
12	272721.6.oct	414600H1	2535	2748
12	272721.6.oct	g2716083	2536	2948
12	272721.6.oct	5426832H1	2534	2810
12	272721.6.oct	3713386H1	2545	2838
12	272721.6.oct	g1577334	2546	2887
12	272721.6.oct	5809476H1	2551	2823
12	272721.6.oct	1680089H1	2552	2768
12	272721.6.oct	g4536024	2556	2944
12	272721.6.oct	232188H1	2561	2894
12	272721.6.oct	231662H1	2563	2743
12	272721.6.oct	232222H1	2563	2731
12	272721.6.oct	g2779419	2563	2930
12	272721.6.oct	2883139T6	2566	2902
12	272721.6.oct	g4452467	2567	2949
12	272721.6.oct	g3405917	2576	2949
12	272721.6.oct	197888H1	1697	1915
12	272721.6.oct	5072033H1	1703	1970
12	272721.6.oct	2613968H1	1703	1939
12	272721.6.oct	962056R1	1703	2252
12	272721.6.oct	962056H1	1703	1993
12	272721.6.oct	6095332H1	1714	2026
12	272721.6.oct	2244263H1	1714	1940
12	272721.6.oct	1865981H1	1732	1991
12	272721.6.oct	5659364H1	1736	1964
12	272721.6.oct	4299096H1	1737	1929
12	272721.6.oct	g1521980	1754	2096
12	272721.6.oct	5665880H1	1759	2008
12	272721.6.oct	3926250H1	1767	2045
12	272721.6.oct	3846571H1	1783	2077
12	272721.6.oct	1752970H1	1791	2049
12	272721.6.oct	2421660H1	1791	2025
12	272721.6.oct	1751279H1	1791	2021
12	272721.6.oct	1294519H1	1795	1991
12	272721.6.oct	5286768H1	1795	1984
12	272721.6.oct	2505278H1	1795	2030
12	272721.6.oct	1851982H1	1802	2081
12	272721.6.oct	5658144H1	1807	2014
12	272721.6.oct	5779914H1	1805	2062
12	272721.6.oct	5531864H1	1828	2086
12	272721.6.oct	4742181H1	1836	2097
12	272721.6.oct	5217356H1	1837	2092
12	272721.6.oct	5159607H1	1839	2100
12	272721.6.oct	5619214H1	1841	2133
12	272721.6.oct	1629148F6	1841	2270
12	272721.6.oct	1629141H1	1841	2049
12	272721.6.oct	5607027H1	1847	2059
12	272721.6.oct	5139939H1	1847	2112
12	272721.6.oct	5679332H1	1850	2128
12	272721.6.oct	5592590H1	1855	2084
12	272721.6.oct	2918819H1	1868	2124
12	272721.6.oct	3256891H1	1869	2123
12	272721.6.oct	1563141H1	1870	2090
12	272721.6.oct	2652784H1	1876	2121
12	272721.6.oct	4371853H1	1876	2152

Table 4

12	272721.6.oct	1399608H1	1878	2128	12	272721.6.oct	6429277H1	2266	2655
12	272721.6.oct	541556H1	1883	2120	12	272721.6.oct	6098047H1	2272	2445
12	272721.6.oct	g2017461	1891	2176	12	272721.6.oct	2308651H1	2272	2524
12	272721.6.oct	4727656H1	1898	2168	12	272721.6.oct	3014469H1	2276	2552
12	272721.6.oct	g3003890	2872	3204	12	272721.6.oct	786983R1	2277	2805
12	272721.6.oct	564887H1	2875	3001	12	272721.6.oct	786983H1	2277	2537
12	272721.6.oct	g2932091	2875	2996	12	272721.6.oct	830695H1	2277	2537
12	272721.6.oct	g500166	2875	3008	12	272721.6.oct	1858762H1	2286	2549
12	272721.6.oct	5525644H2	2908	3182	12	272721.6.oct	g1026279	2293	2564
12	272721.6.oct	1881380T6	2928	3385	12	272721.6.oct	4303854H1	2302	2567
12	272721.6.oct	4941268H1	2228	2490	12	272721.6.oct	1662959H1	2302	2534
12	272721.6.oct	1730067H1	2236	2459	12	272721.6.oct	g1792740	2306	2458
12	272721.6.oct	1294012H1	2252	2504	12	272721.6.oct	3596126H1	2312	2601
12	272721.6.oct	1293975F1	2252	2827	12	272721.6.oct	1689619T6	2307	2903
12	272721.6.oct	1293975H1	2252	2497	12	272721.6.oct	1820290H1	2317	2572
12	272721.6.oct	1272847H1	2252	2500	12	272721.6.oct	1820281H1	2317	2573
12	272721.6.oct	2957128H1	2252	2545	12	272721.6.oct	1873055H1	2324	2555
12	272721.6.oct	2439817H1	2255	2485	12	272721.6.oct	3298163H1	2325	2582
12	272721.6.oct	2040137H1	2255	2519	12	272721.6.oct	805746T1	2326	2906
12	272721.6.oct	2264921H1	2257	2464	12	272721.6.oct	5527791H1	2332	2605
12	272721.6.oct	2268728H1	2257	2487	12	272721.6.oct	3831404H1	2336	2550
12	272721.6.oct	1690407H1	2259	2432	12	272721.6.oct	3840984H1	2338	2587
12	272721.6.oct	763923H1	2260	2536	12	272721.6.oct	805746H1	2338	2573
12	272721.6.oct	4894289H1	1176	1459	12	272721.6.oct	2201471H1	2337	2578
12	272721.6.oct	2556183H1	1181	1433	13	461603.4.oct	2667533H1	1512	1743
12	272721.6.oct	3319651H1	1242	1519	13	461603.4.oct	1862102H1	1523	1792
12	272721.6.oct	831550H1	1250	1452	13	461603.4.oct	2355465H1	1580	1665
12	272721.6.oct	3118134H1	1275	1558	13	461603.4.oct	g3645529	1645	2081
12	272721.6.oct	5902550H1	1283	1580	13	461603.4.oct	3293621H1	1670	1906
12	272721.6.oct	4996858H1	1283	1563	13	461603.4.oct	g2335995	1736	2089
12	272721.6.oct	6113602H1	1295	1617	13	461603.4.oct	3752905H1	1758	2019
12	272721.6.oct	4518784H1	1297	1551	13	461603.4.oct	6094776H1	1908	2151
12	272721.6.oct	1989226H1	1311	1571	13	461603.4.oct	418011H1	1922	2103
12	272721.6.oct	956338H1	1317	1413	13	461603.4.oct	417150H1	1922	2101
12	272721.6.oct	4669770H1	1322	1560	13	461603.4.oct	418870H1	1922	2118
12	272721.6.oct	2821261H1	1324	1630	13	461603.4.oct	413059H1	1922	2129
12	272721.6.oct	1567553H1	1336	1535	13	461603.4.oct	413059R1	1922	2399
12	272721.6.oct	4880720H1	1352	1590	13	461603.4.oct	418870R6	1922	2275
12	272721.6.oct	3881948H1	1359	1622	13	461603.4.oct	417906H1	1922	2125
12	272721.6.oct	3156706H1	1362	1647	13	461603.4.oct	696345H1	1964	2151
12	272721.6.oct	5040118H1	1380	1622	13	461603.4.oct	5694066H1	1987	2177
12	272721.6.oct	3788560H1	1382	1675	13	461603.4.oct	2637796H1	2019	2288
12	272721.6.oct	3806687H1	1389	1646	13	461603.4.oct	3596965H1	2058	2223
12	272721.6.oct	1282584H1	1425	1685	13	461603.4.oct	2673521H1	2077	2325
12	272721.6.oct	1703878H1	1441	1664	13	461603.4.oct	3405821H1	2085	2349
12	272721.6.oct	859573R1	1445	2007	13	461603.4.oct	482251H1	2100	2335
12	272721.6.oct	859573H1	1445	1679	13	461603.4.oct	484926R6	2100	2452
12	272721.6.oct	4848606H2	1446	1695	13	461603.4.oct	5693609H1	2114	2272
12	272721.6.oct	1558344H1	1446	1638	13	461603.4.oct	g1188364	2133	2267
12	272721.6.oct	3720883H1	1454	1628	13	461603.4.oct	3070461H1	2171	2336
12	272721.6.oct	3720892H1	1454	1739	13	461603.4.oct	g2779413	2210	2611
12	272721.6.oct	026143H1	1456	1796	13	461603.4.oct	3356374T6	2218	2437
12	272721.6.oct	5030608H1	1457	1723	13	461603.4.oct	g1780256	2225	2624
12	272721.6.oct	4674029H1	1470	1746	13	461603.4.oct	1756956H1	2404	2651
12	272721.6.oct	2634326H1	1484	1731	13	461603.4.oct	1250711F1	2456	2798
12	272721.6.oct	5830504H1	1489	1704	13	461603.4.oct	5005176H1	2456	2684
12	272721.6.oct	5435568H1	1494	1715	13	461603.4.oct	3001108F6	2554	3018
12	272721.6.oct	290356R6	1494	1974	13	461603.4.oct	1252411H1	2570	2798
12	272721.6.oct	3356346H1	1507	1735	13	461603.4.oct	1951691H1	2583	2801
12	272721.6.oct	3342545H1	1531	1774	13	461603.4.oct	1786802H1	2625	2725
12	272721.6.oct	4847556H1	1552	1806	13	461603.4.oct	1250711H1	2668	2798
12	272721.6.oct	g2156699	1574	1992	13	461603.4.oct	3001108H1	2712	3018
12	272721.6.oct	2503041H1	1574	1797	13	461603.4.oct	3154469H1	2841	3111
12	272721.6.oct	4883822H2	2265	2537	13	461603.4.oct	g4525001	1	365
12	272721.6.oct	1542559H1	2265	2478	13	461603.4.oct	g4148045	2	441
12	272721.6.oct	6430113H1	2266	2655	13	461603.4.oct	g3846311	5	228
12	272721.6.oct	4341009H1	2265	2586	13	461603.4.oct	g4136972	5	365

Table 4

13	461603.4.oct	g1005259	33	338
13	461603.4.oct	2704364T6	44	404
13	461603.4.oct	2254891T6	44	561
13	461603.4.oct	2645122T6	46	510
13	461603.4.oct	g2620015	88	297
13	461603.4.oct	2013516R6	126	582
13	461603.4.oct	4369011H1	145	424
13	461603.4.oct	g2071015	195	603
13	461603.4.oct	5992740H1	210	508
13	461603.4.oct	2013516H1	402	582
13	461603.4.oct	2451916H1	429	656
13	461603.4.oct	2451916F6	429	593
13	461603.4.oct	657176H1	438	686
13	461603.4.oct	492501H1	446	742
13	461603.4.oct	4916755H1	445	723
13	461603.4.oct	1682473H1	450	568
13	461603.4.oct	4662505H1	446	698
13	461603.4.oct	1387072H1	452	597
13	461603.4.oct	2984524H1	454	721
13	461603.4.oct	3298213H1	459	646
13	461603.4.oct	4520106H1	472	717
13	461603.4.oct	803599H1	490	721
13	461603.4.oct	4714474H1	518	770
13	461603.4.oct	3339447H1	534	784
13	461603.4.oct	3339447F6	534	1020
13	461603.4.oct	g1958411	586	1034
13	461603.4.oct	1701488H1	629	804
13	461603.4.oct	2254891R6	657	1102
13	461603.4.oct	4042479H1	685	983
13	461603.4.oct	3231432H1	909	1048
13	461603.4.oct	g3693474	702	1154
13	461603.4.oct	5915013H1	913	1080
13	461603.4.oct	4175420H1	751	1061
13	461603.4.oct	g1067303	959	1150
13	461603.4.oct	5489546H1	1084	1362
13	461603.4.oct	g2783417	1178	1396
13	461603.4.oct	5489828H1	778	1061
13	461603.4.oct	g1968244	1305	1710
13	461603.4.oct	4712047H1	1308	1563
13	461603.4.oct	738669H1	1315	1583
13	461603.4.oct	5152886H1	780	1022
13	461603.4.oct	g3043083	785	846
13	461603.4.oct	g1401520	1341	1597
13	461603.4.oct	5429668H1	1420	1600
13	461603.4.oct	4201935H1	808	1061
13	461603.4.oct	2455871F6	1437	1597
13	461603.4.oct	2911386H1	855	1125
13	461603.4.oct	012355H1	1481	1804
13	461603.4.oct	5544019H1	1492	1695
13	461603.4.oct	2254891H1	871	1102
13	461603.4.oct	g1401616	908	1236
14	332465.2.dec	g340010	1	2969
14	332465.2.dec	3463132F6	1	343
14	332465.2.dec	3463132H1	1	165
14	332465.2.dec	4968429H1	14	190
14	332465.2.dec	3579379H1	30	333
14	332465.2.dec	3579379F6	31	185
14	332465.2.dec	171789H1	77	231
14	332465.2.dec	g1678816	91	451
14	332465.2.dec	2472213F6	149	589
14	332465.2.dec	2472213H1	149	253
14	332465.2.dec	g3180548	184	641
14	332465.2.dec	g3180312	264	641
14	332465.2.dec	5581933H1	360	620
14	332465.2.dec	5669667H1	467	714
14	332465.2.dec	g769408	779	1045
14	332465.2.dec	4531284H1	832	1104
14	332465.2.dec	5544928H1	949	1161
14	332465.2.dec	5615805R8	1117	1510
14	332465.2.dec	4815011H1	1211	1483
14	332465.2.dec	g827150	1285	1543
14	332465.2.dec	g312815	1549	2494
14	332465.2.dec	5283470H1	1626	1869
14	332465.2.dec	4370131H1	1680	1946
14	332465.2.dec	1342780F6	1700	2148
14	332465.2.dec	g2737583	1706	1775
14	332465.2.dec	2505440H2	1833	2074
14	332465.2.dec	1452693H1	1872	2115
14	332465.2.dec	4402015H1	1947	2190
14	332465.2.dec	2453792H1	1952	2170
14	332465.2.dec	3463132T6	2045	2595
14	332465.2.dec	032987H1	2156	2428
14	332465.2.dec	2133608F6	2160	2484
14	332465.2.dec	2133608H1	2160	2423
14	332465.2.dec	g2100470	2231	2703
14	332465.2.dec	g816859	2271	2642
14	332465.2.dec	4968476H1	2320	2577
14	332465.2.dec	3876373H1	2345	2604
14	332465.2.dec	1342780T6	2363	2931
14	332465.2.dec	2292663H1	2371	2624
14	332465.2.dec	3579379T6	2374	2935
14	332465.2.dec	g2783310	2501	2979
14	332465.2.dec	g4074219	2506	2975
14	332465.2.dec	3055317H1	2515	2808
14	332465.2.dec	g2197386	2520	2844
14	332465.2.dec	2012009H1	2530	2632
14	332465.2.dec	g5110989	2533	2976
14	332465.2.dec	g4334290	2537	2968
14	332465.2.dec	2133608T6	2555	2939
14	332465.2.dec	g1678702	2596	2976
14	332465.2.dec	g4888123	2597	2970
14	332465.2.dec	g3778643	2596	2968
14	332465.2.dec	3815651H1	2603	2865
14	332465.2.dec	g4629965	2638	2976
14	332465.2.dec	g2875811	2678	2806
14	332465.2.dec	1334255T6	2694	2935
14	332465.2.dec	1334255H1	2701	2826
14	332465.2.dec	1334255F6	2701	2980
14	332465.2.dec	g2752991	2773	2968
14	332465.2.dec	g2912342	2792	2973
15	445175.3.dec	g2753580	31	93
15	445175.3.dec	g3842531	1	42
15	445175.3.dec	g3835415	1	96
15	445175.3.dec	g4435437	1	144
15	445175.3.dec	g5233483	1	126
15	445175.3.dec	g3154963	1	104
15	445175.3.dec	g4452651	13	263
15	445175.3.dec	g2904826	22	90
15	445175.3.dec	g2818451	1	48
15	445175.3.dec	g2816891	1	148
15	445175.3.dec	5741828H1	1	287
15	445175.3.dec	g1951684	112	331
15	445175.3.dec	g35494	206	2449
15	445175.3.dec	651077H1	988	1254
15	445175.3.dec	3926047F6	1179	1711
15	445175.3.dec	3926047H1	1179	1363
15	445175.3.dec	3926047T6	1552	2070
16	980541.1.dec	g2340868	1	2878
16	980541.1.dec	g2967684	250	2878
16	980541.1.dec	g2586410	402	2878
16	980541.1.dec	6269227H1	1415	1941
16	980541.1.dec	g885094	1763	2107
16	980541.1.dec	g2166303	1923	2377
16	980541.1.dec	g777428	2317	2637

Table 4

16	980541.1.dec	g2525285	2467	2887
16	980541.1.dec	g883161	2494	2869
16	980541.1.dec	g779712	2494	2615
16	980541.1.dec	g2163763	2508	2878
16	980541.1.dec	g873216	2549	2733
16	980541.1.dec	g764624	2544	2923
16	980541.1.dec	g876367	2544	2916
16	980541.1.dec	g830021	2550	2897
16	980541.1.dec	g756279	2551	2813
16	980541.1.dec	g885095	2784	2898
17	237996.1.dec	g5056707	1	334
17	237996.1.dec	4531252H1	1	276
17	237996.1.dec	3614216H1	4	238
17	237996.1.dec	3111306H1	14	222
17	237996.1.dec	3604478H1	200	420
17	237996.1.dec	6152381H1	355	630
17	237996.1.dec	2937960H1	544	802
18	243267.9.dec	429897H1	1	168
18	243267.9.dec	3277737H1	9	250
18	243267.9.dec	5052754H1	134	381
18	243267.9.dec	5984361H1	203	400
18	243267.9.dec	1754639T6	353	616
18	243267.9.dec	1754905F6	360	667
18	243267.9.dec	1754639H1	360	605
19	242082.10.dec	1962272H1	1	267
19	242082.10.dec	1710521H1	9	212
19	242082.10.dec	1710521F6	9	361
19	242082.10.dec	924352H1	77	425
19	242082.10.dec	5121112H1	148	424
19	242082.10.dec	4270649H1	254	505
19	242082.10.dec	1299353H1	286	498
19	242082.10.dec	3373518H1	288	559
19	242082.10.dec	g2159501	304	511
19	242082.10.dec	3748635H1	314	569
19	242082.10.dec	g835896	371	613
19	242082.10.dec	g784665	372	466
19	242082.10.dec	1374464H1	528	747
19	242082.10.dec	5451856H1	569	799
19	242082.10.dec	g1324135	592	1037
19	242082.10.dec	5216316H1	659	906
19	242082.10.dec	g1056590	757	998
19	242082.10.dec	6429773H1	777	1312
19	242082.10.dec	2127293H1	844	1091
19	242082.10.dec	5579027H2	868	1140
19	242082.10.dec	g1276071	900	1263
19	242082.10.dec	3551092H1	905	1206
19	242082.10.dec	1898869H1	918	1197
19	242082.10.dec	g5234067	993	1464
19	242082.10.dec	g2159502	1005	1467
19	242082.10.dec	g5396677	1009	1465
19	242082.10.dec	g5671070	1020	1464
19	242082.10.dec	g1384768	1038	1464
19	242082.10.dec	g3785412	1049	1464
19	242082.10.dec	600663H1	1062	1346
19	242082.10.dec	600663R6	1062	1564
19	242082.10.dec	600663R1	1062	1545
19	242082.10.dec	g2185852	1074	1330
19	242082.10.dec	g1774698	1074	1455
19	242082.10.dec	g2141640	1120	1541
19	242082.10.dec	g564444	1150	1464
19	242082.10.dec	674332H1	1155	1408
19	242082.10.dec	4533148H1	1163	1414
19	242082.10.dec	2867266H1	1164	1463
19	242082.10.dec	2969296H1	1166	1415
19	242082.10.dec	g831436	1169	1428
19	242082.10.dec	2754527H1	1202	1463
19	242082.10.dec	3891815H1	1207	1439
19	242082.10.dec	g2359154	1208	1464
19	242082.10.dec	g3179415	1246	1469
19	242082.10.dec	673956H1	1283	1547
19	242082.10.dec	5482918H1	1286	1535
19	242082.10.dec	1395173T6	1287	1433
19	242082.10.dec	2202416H1	1301	1558
19	242082.10.dec	2202416F6	1301	1554
19	242082.10.dec	g1765329	1314	1441
19	242082.10.dec	g1190219	1368	1716
19	242082.10.dec	600663F1	1369	1973
19	242082.10.dec	g2589750	1404	1464
19	242082.10.dec	2133344H1	1408	1545
19	242082.10.dec	5024752H1	1428	1522
19	242082.10.dec	632098H1	1457	1724
19	242082.10.dec	2202416T6	1466	1953
19	242082.10.dec	3091754H1	1480	1752
19	242082.10.dec	1926130H1	1487	1690
19	242082.10.dec	1926130R6	1487	1973
19	242082.10.dec	2292755H1	1505	1753
19	242082.10.dec	2867724H1	1507	1805
19	242082.10.dec	g5438605	1519	1981
19	242082.10.dec	g728298	1521	1734
19	242082.10.dec	g4003740	1527	1981
19	242082.10.dec	g1678437	1539	1873
19	242082.10.dec	g3445912	1548	1976
19	242082.10.dec	g4188129	1548	1977
19	242082.10.dec	g4002844	1552	1974
19	242082.10.dec	g1686101	1559	1976
19	242082.10.dec	466459T6	1594	1932
19	242082.10.dec	466459H1	1602	1828
19	242082.10.dec	466459R6	1603	1973
19	242082.10.dec	468718H1	1603	1828
19	242082.10.dec	g2186213	1621	1988
19	242082.10.dec	1220035R6	1671	1973
19	242082.10.dec	3881469H1	1682	1964
19	242082.10.dec	g1266171	1694	1973
19	242082.10.dec	059532H1	1699	1905
19	242082.10.dec	g1189494	1711	1974
19	242082.10.dec	g1056493	1751	1988
19	242082.10.dec	g3232610	1797	1985
19	242082.10.dec	g1226704	1839	1978
20	019239.1.dec	g2037390	1	291
20	019239.1.dec	1297333F6	1	491
20	019239.1.dec	1297333H1	1	263
20	019239.1.dec	3331976H1	407	597
20	019239.1.dec	3040041F6	523	770
20	019239.1.dec	3040041H1	523	788
20	019239.1.dec	4938596H1	658	815
20	019239.1.dec	g677095	684	892
20	019239.1.dec	503922H1	692	921
20	019239.1.dec	503922R1	692	1098
20	019239.1.dec	5318750H1	866	1056
20	019239.1.dec	3693495H1	888	1098
20	019239.1.dec	3693495F6	888	1331
20	019239.1.dec	618665H1	1020	1287
20	019239.1.dec	2158372H1	1020	1273
20	019239.1.dec	1297470F6	1142	1583
20	019239.1.dec	689278H1	1142	1365
20	019239.1.dec	1297470H1	1142	1286
20	019239.1.dec	3775993H1	1142	1393
20	019239.1.dec	1297470T6	1163	1789
20	019239.1.dec	g2557145	1210	1404
20	019239.1.dec	6343003H1	1232	1451
20	019239.1.dec	4769071H1	1271	1509
20	019239.1.dec	3040041T6	1302	1754
20	019239.1.dec	2840627F6	1510	2050
20	019239.1.dec	2840627H1	1510	1760

Table 4

20	019239.1.dec	g703791	1567	1844
20	019239.1.dec	3022511H1	1730	1972
20	019239.1.dec	3693495T6	1858	2211
20	019239.1.dec	g703718	1941	2323
20	019239.1.dec	g2657422	1936	2321
20	019239.1.dec	g2904422	1944	2328
20	019239.1.dec	g3417623	1956	2328
20	019239.1.dec	2945454H1	1968	2268
20	019239.1.dec	g3331297	1970	2328
21	899943.1.dec	3117949H1	3144	3323
21	899943.1.dec	2756752H1	3200	3462
21	899943.1.dec	495759F1	3217	3767
21	899943.1.dec	1332986T6	3230	3287
21	899943.1.dec	3297117H1	3311	3563
21	899943.1.dec	2485552H1	1	212
21	899943.1.dec	g3869258	157	4209
21	899943.1.dec	g3869256	157	4209
21	899943.1.dec	2693067H1	514	768
21	899943.1.dec	2535607H1	793	1049
21	899943.1.dec	3502278H1	1004	1306
21	899943.1.dec	g1779649	1165	1612
21	899943.1.dec	495759R1	1254	1720
21	899943.1.dec	495759R6	1255	1621
21	899943.1.dec	495759H1	1255	1499
21	899943.1.dec	494011R1	1627	2049
21	899943.1.dec	494011R6	1627	1996
21	899943.1.dec	494011H1	1627	1857
21	899943.1.dec	g3896433	1636	2013
21	899943.1.dec	994895R1	1671	2179
21	899943.1.dec	994895H1	1671	1941
21	899943.1.dec	680754H1	1716	1981
21	899943.1.dec	2367903H1	2743	2973
21	899943.1.dec	3488220H1	1729	2009
21	899943.1.dec	1332986F6	1799	2106
21	899943.1.dec	1332986H1	1799	2031
21	899943.1.dec	1964279H1	1900	2175
21	899943.1.dec	g1357787	2020	2620
21	899943.1.dec	5874572H1	2031	2289
21	899943.1.dec	2598088F6	2092	2692
21	899943.1.dec	g573567	2092	2455
21	899943.1.dec	2598088H1	2092	2210
21	899943.1.dec	2598088T6	2749	3316
21	899943.1.dec	6409839H1	2142	2685
21	899943.1.dec	5035552H1	2206	2458
21	899943.1.dec	1997937R6	2232	2728
21	899943.1.dec	1997937H1	2232	2503
21	899943.1.dec	g3887783	2268	2695
21	899943.1.dec	1997937T6	2320	2860
21	899943.1.dec	g1280977	2327	2848
21	899943.1.dec	155875R6	2327	2806
21	899943.1.dec	155875H1	2327	2539
21	899943.1.dec	6096636H1	2386	2589
21	899943.1.dec	2370164T6	2763	3288
21	899943.1.dec	5876310H1	2404	2706
21	899943.1.dec	4895030H1	2404	2686
21	899943.1.dec	g1941651	2406	2849
21	899943.1.dec	g658182	2431	2678
21	899943.1.dec	g2718978	2444	2885
21	899943.1.dec	5298571H1	2458	2721
21	899943.1.dec	5298771H1	2458	2706
21	899943.1.dec	5298612H1	2459	2574
21	899943.1.dec	4749511H1	2459	2740
21	899943.1.dec	g715365	2457	2775
21	899943.1.dec	g1471133	2474	2886
21	899943.1.dec	6555238H1	2483	3021
21	899943.1.dec	6556278H1	2483	2986
21	899943.1.dec	2913641H1	2517	2778
21	899943.1.dec	6400248H1	2535	2708
21	899943.1.dec	g1719353	2544	2985
21	899943.1.dec	g1960091	2579	3079
21	899943.1.dec	2367903F6	2743	3186
21	899943.1.dec	494011F1	2790	3333
21	899943.1.dec	1398685H1	2833	3081
21	899943.1.dec	1380634H1	2837	3083
21	899943.1.dec	5138789H1	2847	3123
21	899943.1.dec	5067594H1	2856	3041
21	899943.1.dec	494011T6	2868	3293
21	899943.1.dec	g2051891	2874	3336
21	899943.1.dec	g4738083	2883	3335
21	899943.1.dec	6489656H1	2893	3002
21	899943.1.dec	g3419253	2900	3333
21	899943.1.dec	g5656805	2920	3333
21	899943.1.dec	g1444847	2925	3334
21	899943.1.dec	g3416160	2941	3337
21	899943.1.dec	g1719354	2952	3342
21	899943.1.dec	g1780421	2962	3338
21	899943.1.dec	g654349	3042	3329
21	899943.1.dec	g758975	3051	3367
21	899943.1.dec	g564984	3050	3333
21	899943.1.dec	g1357788	3057	3353
21	899943.1.dec	g2931035	3072	3333
21	899943.1.dec	155875T6	3074	3724
21	899943.1.dec	3874011H1	3079	3346
21	899943.1.dec	g1190099	3111	3328
21	899943.1.dec	g2959267	3312	3777
21	899943.1.dec	g3836196	3344	3771
21	899943.1.dec	154612T6	3375	3733
21	899943.1.dec	g2877501	3399	3771
21	899943.1.dec	g3838447	3423	3771
21	899943.1.dec	g1187596	3476	3767
21	899943.1.dec	6192804H1	3498	3767
21	899943.1.dec	6194735H1	3498	3767
21	899943.1.dec	6194703H1	3498	3752
21	899943.1.dec	495759T6	3521	3724
21	899943.1.dec	g4737879	3527	3767
21	899943.1.dec	g758939	3527	3748
21	899943.1.dec	g3895731	3527	3771
21	899943.1.dec	g1079906	3542	3817
21	899943.1.dec	767355H1	3676	3926
21	899943.1.dec	g1115031	3784	4214
22	443551.1.dec	381281H1	1	276
22	443551.1.dec	491740R1	1	496
22	443551.1.dec	491740H1	1	233
22	443551.1.dec	5545931T6	231	680
22	443551.1.dec	5511796H1	388	617
22	443551.1.dec	2727051H1	416	710
22	443551.1.dec	g3888654	417	693
22	443551.1.dec	4307033H1	501	639
22	443551.1.dec	491740R6	1	403
22	443551.1.dec	g1196460	1	494
22	443551.1.dec	g2522501	351	499
23	897957.1.dec	1332888H1	110	341
23	897957.1.dec	g2595651	1	335
23	897957.1.dec	2862618T6	1	569
23	897957.1.dec	1332888F6	110	562
23	897957.1.dec	452282H1	311	525
23	897957.1.dec	g1951500	443	756
23	897957.1.dec	g3245520	599	1047
23	897957.1.dec	g2873952	701	1041
23	897957.1.dec	4797192F6	794	1163
23	897957.1.dec	1330155H1	110	344
24	900911.1.dec	1398471H1	1	238
24	900911.1.dec	2694772F6	125	338
24	900911.1.dec	g4690049	1	195

Table 4

24	900911.1.dec	g3034163	1	86
24	900911.1.dec	1398471F6	1	410
24	900911.1.dec	2694772H1	126	337
24	900911.1.dec	4018267H1	135	429
24	900911.1.dec	4018267F6	135	426
24	900911.1.dec	2927224H2	209	509
24	900911.1.dec	3382640H1	351	440
24	900911.1.dec	2110417H1	409	676
24	900911.1.dec	1399832H1	1	227
25	999296.1.dec	569710T6	225	536
25	999296.1.dec	1914106H1	219	469
25	999296.1.dec	g2317768	1	543
25	999296.1.dec	1923296H1	1	276
25	999296.1.dec	1923488H1	1	255
25	999296.1.dec	4768094T6	42	583
25	999296.1.dec	g2522505	86	250
25	999296.1.dec	1923488T6	96	557
25	999296.1.dec	1335071H1	95	341
25	999296.1.dec	g3896841	156	513
25	999296.1.dec	5085341H1	162	365
25	999296.1.dec	5643520R8	166	440
25	999296.1.dec	4874348H1	174	449
25	999296.1.dec	1784584H1	195	460
25	999296.1.dec	2912050H1	229	532
25	999296.1.dec	3322736H1	379	646
25	999296.1.dec	1923488R6	1	405
26	442286.1.dec	1379688F6	1	322
26	442286.1.dec	1375814F1	1	381
26	442286.1.dec	g715910	11	316
26	442286.1.dec	1379688T6	41	580
26	442286.1.dec	g697373	372	587
26	442286.1.dec	3790789H1	407	656
26	442286.1.dec	1375814H1	1	240
26	442286.1.dec	1379688H1	1	222
27	901978.1.dec	446871R6	565	849
27	901978.1.dec	3128415F6	1	466
27	901978.1.dec	4031889H1	1	234
27	901978.1.dec	4031889F6	1	462
27	901978.1.dec	5668166H1	100	338
27	901978.1.dec	4129275H2	135	401
27	901978.1.dec	6553482H1	148	447
27	901978.1.dec	g2154384	209	447
27	901978.1.dec	2997522H1	213	468
27	901978.1.dec	g1696284	220	560
27	901978.1.dec	3295381H1	223	461
27	901978.1.dec	2007652H1	226	416
27	901978.1.dec	2007652R6	226	485
27	901978.1.dec	2007652T6	226	454
27	901978.1.dec	g2141617	285	485
27	901978.1.dec	2827425H2	303	511
27	901978.1.dec	4528583F6	397	794
27	901978.1.dec	4528583H1	398	643
27	901978.1.dec	444179R6	570	978
27	901978.1.dec	446871H1	570	908
27	901978.1.dec	g4970407	852	1278
27	901978.1.dec	2715520F6	891	1358
27	901978.1.dec	g1442764	989	1214
27	901978.1.dec	444179H1	565	870
27	901978.1.dec	2715520H1	886	1120
28	479346.1.dec	4003594H1	64	265
28	479346.1.dec	493568R6	1132	1503
28	479346.1.dec	1437357H1	709	962
28	479346.1.dec	g4331920	78	252
28	479346.1.dec	g4311455	1	337
28	479346.1.dec	g2953332	1	224
28	479346.1.dec	6172546H1	1	300
28	479346.1.dec	3256006H1	1	261
28	479346.1.dec	6477244H1	65	627
28	479346.1.dec	6484883H1	172	748
28	479346.1.dec	5347152H1	265	513
28	479346.1.dec	4044595H1	282	624
28	479346.1.dec	g1844136	286	628
28	479346.1.dec	495945H1	248	498
28	479346.1.dec	495945R6	295	796
28	479346.1.dec	270352H1	329	675
28	479346.1.dec	2556546F6	342	829
28	479346.1.dec	2556546H1	342	587
28	479346.1.dec	4003594R6	359	841
28	479346.1.dec	g2156015	388	624
28	479346.1.dec	5607740H1	408	655
28	479346.1.dec	g992251	374	696
28	479346.1.dec	5629488H1	434	687
28	479346.1.dec	g1198731	634	862
28	479346.1.dec	1437357F6	711	1213
28	479346.1.dec	g814289	870	1286
28	479346.1.dec	493568R1	1135	1577
28	479346.1.dec	493568H1	1135	1369
28	479346.1.dec	g1060060	1343	1512
28	479346.1.dec	2208031H1	1459	1701
29	481750.1.dec	g2156002	445	566
29	481750.1.dec	6121404H1	1174	1645
29	481750.1.dec	6118209H1	1174	1669
29	481750.1.dec	g5370030	2067	2453
29	481750.1.dec	6051387J1	1788	2301
29	481750.1.dec	5813882H1	175	326
29	481750.1.dec	g2328990	735	986
29	481750.1.dec	g4573711	2069	2459
29	481750.1.dec	g1921216	2068	2459
29	481750.1.dec	5814345H1	175	399
29	481750.1.dec	6118412H1	1174	1669
29	481750.1.dec	5819550H1	175	254
29	481750.1.dec	5821510H1	175	410
29	481750.1.dec	3392427H1	726	1011
29	481750.1.dec	310596H1	1353	1554
29	481750.1.dec	5108871H1	1	246
29	481750.1.dec	1914622H1	90	331
29	481750.1.dec	4028002H1	131	413
29	481750.1.dec	5821402H1	134	436
29	481750.1.dec	5813479H1	134	414
29	481750.1.dec	4784933H2	143	409
29	481750.1.dec	4820753F6	164	736
29	481750.1.dec	4820753H1	164	433
29	481750.1.dec	3561080H1	165	291
29	481750.1.dec	258608H1	168	349
29	481750.1.dec	1390606H1	196	456
29	481750.1.dec	3199745H1	278	503
29	481750.1.dec	g3229581	464	833
29	481750.1.dec	g3118358	508	985
29	481750.1.dec	4200727H1	648	949
29	481750.1.dec	426001H1	687	950
29	481750.1.dec	429190H1	682	805
29	481750.1.dec	424948H1	687	927
29	481750.1.dec	g1995962	688	1055
29	481750.1.dec	3392402F6	729	1089
29	481750.1.dec	3392402H1	728	1030
29	481750.1.dec	g2112377	833	1273
29	481750.1.dec	6560051H1	833	1383
29	481750.1.dec	1691842H1	925	1167
29	481750.1.dec	1691166H1	1111	1203
29	481750.1.dec	6051387H1	1184	1768
29	481750.1.dec	5004434H1	1223	1433
29	481750.1.dec	2041133H1	1488	1723
29	481750.1.dec	g1745471	1508	1897
29	481750.1.dec	g1291764	1572	2107

Table 4

29	481750.1.dec	3392402T6	1656	2164
29	481750.1.dec	4181819T8	1701	2172
29	481750.1.dec	g3960862	1725	2116
29	481750.1.dec	6051495J1	1763	2337
29	481750.1.dec	3514153H1	1774	2042
29	481750.1.dec	1793831R6	1795	2194
29	481750.1.dec	1793831H1	1795	2095
29	481750.1.dec	4129281T6	1886	2251
29	481750.1.dec	3725148H1	1901	2193
29	481750.1.dec	4820753T6	1929	2464
29	481750.1.dec	1793831T6	1946	2458
29	481750.1.dec	g1745418	1953	2193
29	481750.1.dec	6454265H1	1971	2424
29	481750.1.dec	g1241685	1995	2108
29	481750.1.dec	g4573702	2061	2494
29	481750.1.dec	3705964H1	2069	2338
29	481750.1.dec	g2112268	2085	2495
29	481750.1.dec	3276661H1	2251	2494
29	481750.1.dec	6051495H1	1163	1638
29	481750.1.dec	5814635H1	175	391
30	900917.2.dec	492415R6	1	469
30	900917.2.dec	492415H1	1	226
30	900917.2.dec	g1265162	8	427
30	900917.2.dec	3365206H1	11	246
30	900917.2.dec	3110432H1	46	322
30	900917.2.dec	3469861H1	99	369
31	999415.1.dec	2554389F6	1	428
31	999415.1.dec	2554389H1	1	251
31	999415.1.dec	5347358H1	2	261
31	999415.1.dec	2554389T6	6	393
31	999415.1.dec	2733444H1	46	287
31	999415.1.dec	g1637277	159	376
31	999415.1.dec	2767114F6	281	702
31	999415.1.dec	5791156H1	380	682
32	900680.2.dec	2882704F6	1	490
32	900680.2.dec	5518860H1	21	294
32	900680.2.dec	263959H1	53	361
32	900680.2.dec	269967H1	55	367
32	900680.2.dec	g681529	56	376
32	900680.2.dec	263959R6	56	500
32	900680.2.dec	3385441H1	57	304
32	900680.2.dec	6486823H1	62	645
32	900680.2.dec	4742910H1	85	350
32	900680.2.dec	4526902H1	90	362
32	900680.2.dec	g680873	325	609
32	900680.2.dec	180567R6	351	796
32	900680.2.dec	180718R6	417	796
32	900680.2.dec	180567H1	561	814
32	900680.2.dec	3742288H1	736	1012
32	900680.2.dec	267454H1	77	436
32	900680.2.dec	2882704H1	2	260
32	900680.2.dec	180718H1	688	780
33	902791.3.dec	g2350726	1752	2098
33	902791.3.dec	g666724	1059	1324
33	902791.3.dec	g712297	1903	2098
33	902791.3.dec	4375518H1	782	1044
33	902791.3.dec	g1382485	1736	2168
33	902791.3.dec	365699H1	1727	1863
33	902791.3.dec	g5633687	1745	2168
33	902791.3.dec	1989220H1	1732	1934
33	902791.3.dec	g2156365	1748	2170
33	902791.3.dec	g2165832	1752	2173
33	902791.3.dec	3728909H1	1771	2085
33	902791.3.dec	g3178980	1788	2170
33	902791.3.dec	4729789H1	1800	2064
33	902791.3.dec	4858660F6	1792	2160
33	902791.3.dec	g756133	1815	2145
33	902791.3.dec	3429917H1	1821	2046
33	902791.3.dec	1449768F6	1855	2167
33	902791.3.dec	1449751R1	1865	2167
33	902791.3.dec	4858660H1	1900	2159
33	902791.3.dec	3519949H1	1920	2166
33	902791.3.dec	873395H1	1923	2104
33	902791.3.dec	g2350764	1946	2167
33	902791.3.dec	176175H1	2052	2167
33	902791.3.dec	898974H1	1601	1790
33	902791.3.dec	g848299	1396	1723
33	902791.3.dec	6512815H1	1040	1595
33	902791.3.dec	4374584H1	782	1043
33	902791.3.dec	898974T1	1921	2047
33	902791.3.dec	g1367706	1575	1842
33	902791.3.dec	141702H1	1563	1787
33	902791.3.dec	450088H1	764	995
33	902791.3.dec	3508596H1	1	212
33	902791.3.dec	1390970H1	1	218
33	902791.3.dec	4575303H1	40	321
33	902791.3.dec	g1964700	85	525
33	902791.3.dec	3974703H1	86	362
33	902791.3.dec	6051917J1	143	615
33	902791.3.dec	6133494H1	172	469
33	902791.3.dec	071200H1	204	383
33	902791.3.dec	g761186	265	582
33	902791.3.dec	3210822F6	422	948
33	902791.3.dec	3210822H1	423	603
33	902791.3.dec	4232346H2	501	748
33	902791.3.dec	1946681H1	506	737
33	902791.3.dec	5078577H1	546	773
33	902791.3.dec	2947767H1	554	858
33	902791.3.dec	6364645H1	656	946
33	902791.3.dec	1709770H1	688	909
33	902791.3.dec	450088R6	772	1110
33	902791.3.dec	450088R1	772	1365
33	902791.3.dec	1420607H1	824	1056
33	902791.3.dec	3973901H1	831	1142
33	902791.3.dec	4891459H1	950	1226
33	902791.3.dec	1676067H1	1012	1258
33	902791.3.dec	1676067F6	1012	1524
33	902791.3.dec	3370236H1	1032	1157
33	902791.3.dec	2557147H1	1034	1272
33	902791.3.dec	g2159741	1042	1437
33	902791.3.dec	2227620H1	1123	1363
33	902791.3.dec	g4982966	1139	1595
33	902791.3.dec	3527710H1	1183	1500
33	902791.3.dec	g2017626	1208	1549
33	902791.3.dec	663715H1	1207	1463
33	902791.3.dec	1742349H1	1290	1585
33	902791.3.dec	4974283H1	1302	1572
33	902791.3.dec	4889859H1	1311	1593
33	902791.3.dec	6267412H1	1359	1841
33	902791.3.dec	6599047H1	1397	1925
33	902791.3.dec	2958222H1	1401	1714
33	902791.3.dec	393523T6	1414	1796
33	902791.3.dec	393523R6	1414	1842
33	902791.3.dec	g5660784	1406	1856
33	902791.3.dec	3507311H1	1457	1750
33	902791.3.dec	4584726H1	1459	1750
33	902791.3.dec	1676067T6	1490	2106
33	902791.3.dec	450088F1	1497	2167
33	902791.3.dec	g3038831	1521	1846
33	902791.3.dec	g3038830	1527	1847
33	902791.3.dec	g712296	1543	1785
33	902791.3.dec	g756240	1543	1783
33	902791.3.dec	4829913H2	1550	1844
33	902791.3.dec	1863570H1	1561	1855

Table 4

33	902791.3.dec	1863570F6	1561	1967
33	902791.3.dec	6436307H1	1553	1990
33	902791.3.dec	g5545931	1573	1961
33	902791.3.dec	3210822T6	1587	2129
33	902791.3.dec	g2657609	1577	1943
33	902791.3.dec	g3254813	1577	1833
33	902791.3.dec	141702R1	1598	2109
33	902791.3.dec	2317494H1	1641	1932
33	902791.3.dec	322090H1	1648	1909
33	902791.3.dec	g3094372	1670	2166
33	902791.3.dec	108881H1	1660	1920
33	902791.3.dec	108880H1	1661	1919
33	902791.3.dec	492499H1	1676	1993
33	902791.3.dec	1917344H1	1698	2002
33	902791.3.dec	3046230H1	1707	2001
33	902791.3.dec	g659991	1730	2168
33	902791.3.dec	g3836821	1731	2167
33	902791.3.dec	g2354545	1733	2167
33	902791.3.dec	g848165	665	831
33	902791.3.dec	1647786H1	1007	1208
33	902791.3.dec	g848164	1777	2098
33	902791.3.dec	5741921H1	1577	1844
33	902791.3.dec	g3056452	1848	2033
33	902791.3.dec	1405954F6	1578	2008
33	902791.3.dec	2663411H1	1353	1587
33	902791.3.dec	5541935H1	821	1025
33	902791.3.dec	g2217589	1694	2097
33	902791.3.dec	095210H1	140	361
33	902791.3.dec	1449768H1	1803	2082
33	902791.3.dec	1405954H1	1578	1837
33	902791.3.dec	g848230	1748	2075
33	902791.3.dec	1449751H1	1803	2032
33	902791.3.dec	3687926H1	1191	1471
33	902791.3.dec	962224H1	1524	1808
34	053826.1.dec	g2943715	1	1445
34	053826.1.dec	6487571H1	657	1158
34	053826.1.dec	1544823H1	692	895
34	053826.1.dec	1544823R6	692	1178
34	053826.1.dec	g4686743	876	1324
34	053826.1.dec	6476403H1	995	1520
35	204932.4.dec	g4264955	1476	1714
35	204932.4.dec	541266H1	1481	1680
35	204932.4.dec	g4150552	1493	1714
35	204932.4.dec	g3108908	1500	1721
35	204932.4.dec	4188420H1	1517	1721
35	204932.4.dec	g2197690	1557	1715
35	204932.4.dec	5097766H1	651	904
35	204932.4.dec	6015096H1	656	782
35	204932.4.dec	1479435F6	672	1239
35	204932.4.dec	1479435H1	679	891
35	204932.4.dec	1479435H6	679	855
35	204932.4.dec	751351H1	704	935
35	204932.4.dec	3028675H1	723	1021
35	204932.4.dec	2304351H1	737	1003
35	204932.4.dec	016985H1	740	998
35	204932.4.dec	019239H1	740	846
35	204932.4.dec	700106H1	755	979
35	204932.4.dec	g2011955	792	1077
35	204932.4.dec	3970532H1	799	1090
35	204932.4.dec	4120265H1	798	1066
35	204932.4.dec	3713639H1	851	1117
35	204932.4.dec	5784260H1	887	1177
35	204932.4.dec	5786467H1	887	1175
35	204932.4.dec	5790638H1	887	1198
35	204932.4.dec	5785877H1	887	1173
35	204932.4.dec	5788012H1	887	1168
35	204932.4.dec	5786237H1	887	1163
35	204932.4.dec	5784025H1	887	1156
35	204932.4.dec	5790319H1	887	1153
35	204932.4.dec	4855759H2	894	1154
35	204932.4.dec	4864225H1	897	1156
35	204932.4.dec	3151981H1	910	1194
35	204932.4.dec	4066587H1	918	986
35	204932.4.dec	5942136H1	920	1194
35	204932.4.dec	4753538H1	926	1153
35	204932.4.dec	4858795H1	961	1194
35	204932.4.dec	4274791H1	997	1288
35	204932.4.dec	3965157H1	1029	1320
35	204932.4.dec	3965144H1	1029	1207
35	204932.4.dec	4547779H1	1039	1304
35	204932.4.dec	5297978H1	1055	1311
35	204932.4.dec	5297878H1	1055	1311
35	204932.4.dec	6355143H1	1057	1366
35	204932.4.dec	4319912H1	1078	1362
35	204932.4.dec	2353679F6	1087	1704
35	204932.4.dec	2353679H1	1087	1304
35	204932.4.dec	430232H1	1091	1388
35	204932.4.dec	1320009T6	1097	1674
35	204932.4.dec	1690478T6	1112	1676
35	204932.4.dec	3343643H1	1124	1375
35	204932.4.dec	3285682H1	1128	1367
35	204932.4.dec	1998431R6	1133	1650
35	204932.4.dec	1998431H1	1133	1407
35	204932.4.dec	5991660H1	1140	1378
35	204932.4.dec	5882654H1	1145	1427
35	204932.4.dec	732402H1	1158	1342
35	204932.4.dec	1479435T6	1163	1675
35	204932.4.dec	1998431T6	1181	1675
35	204932.4.dec	1889468H1	1187	1435
35	204932.4.dec	1889585H1	1187	1428
35	204932.4.dec	4916307H1	1208	1510
35	204932.4.dec	3200452H1	1209	1455
35	204932.4.dec	819071H1	1219	1480
35	204932.4.dec	2235851T6	1232	1688
35	204932.4.dec	2353679T6	1235	1672
35	204932.4.dec	1355911H1	1257	1510
35	204932.4.dec	g3678268	1264	1722
35	204932.4.dec	2369972H1	1271	1506
35	204932.4.dec	2369922H1	1271	1499
35	204932.4.dec	1289944T6	1289	1687
35	204932.4.dec	g4630098	1307	1720
35	204932.4.dec	6268273H1	1306	1549
35	204932.4.dec	g1330828	1312	1724
35	204932.4.dec	3860841H1	1337	1618
35	204932.4.dec	g3240929	1337	1722
35	204932.4.dec	3868841H1	1337	1581
35	204932.4.dec	g2347994	1337	1722
35	204932.4.dec	g2343842	1349	1716
35	204932.4.dec	g2189625	1352	1719
35	204932.4.dec	g4070372	1380	1714
35	204932.4.dec	g5449165	1383	1722
35	204932.4.dec	1851746F6	1410	1722
35	204932.4.dec	1851746H1	1410	1695
35	204932.4.dec	1851746T6	1410	1682
35	204932.4.dec	1725847T6	1411	1667
35	204932.4.dec	g5113636	1420	1718
35	204932.4.dec	g2278725	1426	1722
35	204932.4.dec	g2030838	1428	1714
35	204932.4.dec	g3096526	1432	1722
35	204932.4.dec	g1792426	1439	1722
35	204932.4.dec	g518176	1462	1722
35	204932.4.dec	3583757H1	1	210
35	204932.4.dec	1320009F6	11	507
35	204932.4.dec	1320009H1	11	249

Table 4

35	204932.4.dec	4936650H1	11	145
35	204932.4.dec	4874178H1	75	338
35	204932.4.dec	4960796H1	188	463
35	204932.4.dec	4984123H1	241	534
35	204932.4.dec	2791753H1	246	544
35	204932.4.dec	2235851F6	249	672
35	204932.4.dec	2235851H1	249	500
35	204932.4.dec	5314874H1	294	540
35	204932.4.dec	1690478F6	324	902
35	204932.4.dec	1690478H1	324	549
35	204932.4.dec	2623640H1	351	571
35	204932.4.dec	2115765H1	364	632
35	204932.4.dec	1559647H1	372	488
35	204932.4.dec	3111240H1	376	614
35	204932.4.dec	5942343H1	404	682
35	204932.4.dec	1434326H1	407	652
35	204932.4.dec	4434460H1	407	677
35	204932.4.dec	5942375H1	408	682
35	204932.4.dec	1725847F6	413	701
35	204932.4.dec	1725847H1	413	631
35	204932.4.dec	712325H1	415	581
35	204932.4.dec	6118873H1	459	1025
35	204932.4.dec	1344768H1	493	744
35	204932.4.dec	3211184H1	502	696
35	204932.4.dec	3955839H1	503	788
35	204932.4.dec	1341743H1	542	768
35	204932.4.dec	3845847H1	554	858
35	204932.4.dec	2484267H1	609	740
35	204932.4.dec	3046336H1	643	916
35	204932.4.dec	3273541H1	651	888
36	400607.19.dec	5372609H1	1016	1264
36	400607.19.dec	5522590R6	441	917
36	400607.19.dec	6051163J1	1075	1600
36	400607.19.dec	044309H1	1151	1443
36	400607.19.dec	3071036T6	533	675
36	400607.19.dec	6452713H1	797	1087
36	400607.19.dec	265709H1	837	1144
36	400607.19.dec	g1198101	1196	1427
36	400607.19.dec	6051163H1	864	1366
36	400607.19.dec	g1938960	861	1277
36	400607.19.dec	5466843H1	948	1155
36	400607.19.dec	5090216H1	989	1255
36	400607.19.dec	703912H1	1216	1446
36	400607.19.dec	g2879168	1223	1447
36	400607.19.dec	1542073H1	1333	1553
36	400607.19.dec	5735728H1	1345	1622
36	400607.19.dec	4884751H1	1477	1660
36	400607.19.dec	4970739H1	25	313
36	400607.19.dec	4970746H1	27	318
36	400607.19.dec	3371686H1	9	250
36	400607.19.dec	g1775491	32	121
36	400607.19.dec	6540907H1	59	520
36	400607.19.dec	6115923H1	58	370
36	400607.19.dec	5522590H1	69	323
36	400607.19.dec	4575104H1	349	622
36	400607.19.dec	3455027H1	1	178
36	400607.19.dec	5628012H1	9	266
36	400607.19.dec	593471H1	8	253
36	400607.19.dec	3071036H1	9	246
36	400607.19.dec	3071036F6	9	359
37	444248.7.dec	170389H1	21	240
37	444248.7.dec	1655929H1	18	208
37	444248.7.dec	1439566H1	62	315
37	444248.7.dec	2994742H1	27	293
37	444248.7.dec	3213073H1	54	335
37	444248.7.dec	2898196H1	17	292
37	444248.7.dec	1563083H1	23	228
37	444248.7.dec	1532422H1	15	212
37	444248.7.dec	1533172H1	15	233
37	444248.7.dec	778480H1	16	221
37	444248.7.dec	776391H1	16	237
37	444248.7.dec	3237823H1	17	259
37	444248.7.dec	1695590H1	14	239
37	444248.7.dec	2998348H1	16	293
37	444248.7.dec	369401H1	21	182
37	444248.7.dec	1438256H1	18	287
37	444248.7.dec	1692514H1	120	333
37	444248.7.dec	1238138H1	1	286
37	444248.7.dec	3475673H1	9	310
37	444248.7.dec	3392650H1	11	318
37	444248.7.dec	4677717H1	12	314
37	444248.7.dec	1515147H1	12	212
37	444248.7.dec	5076477H1	12	297
37	444248.7.dec	3392320H1	12	315
37	444248.7.dec	1695554H1	12	255
37	444248.7.dec	3775912H1	12	341
37	444248.7.dec	1436523H1	12	285
37	444248.7.dec	1435848F6	14	480
37	444248.7.dec	4048084H1	12	169
37	444248.7.dec	2661035H1	12	280
37	444248.7.dec	1437814H1	12	300
37	444248.7.dec	2632679H1	12	300
37	444248.7.dec	2681312H1	15	350
37	444248.7.dec	2347774H1	12	290
37	444248.7.dec	994711H1	14	255
37	444248.7.dec	4380030H1	15	297
37	444248.7.dec	5158504H1	13	283
37	444248.7.dec	366639H1	13	316
37	444248.7.dec	1695566H1	14	277
37	444248.7.dec	3046267H1	16	340
37	444248.7.dec	369624H1	13	359
37	444248.7.dec	g610262	14	278
37	444248.7.dec	2180115H1	15	306
37	444248.7.dec	171713H1	14	224
37	444248.7.dec	369649H1	15	341
37	444248.7.dec	2180095H1	15	315
37	444248.7.dec	775276H1	15	262
37	444248.7.dec	1438177H1	16	311
37	444248.7.dec	2860455H1	16	296
37	444248.7.dec	2896853H1	17	288
37	444248.7.dec	369074H1	17	324
37	444248.7.dec	1434834H1	17	296
37	444248.7.dec	4643424H1	16	297
37	444248.7.dec	2648482H1	16	293
37	444248.7.dec	1661048H1	17	293
37	444248.7.dec	1821754H1	16	260
37	444248.7.dec	3118115H1	18	340
37	444248.7.dec	3340141H1	18	296
37	444248.7.dec	2182036H1	18	302
37	444248.7.dec	2634076H1	18	304
37	444248.7.dec	2897344H1	19	321
37	444248.7.dec	2897344F6	19	474
37	444248.7.dec	1437855H1	21	296
37	444248.7.dec	1692892H1	20	263
37	444248.7.dec	3339956H1	21	311
37	444248.7.dec	2461339H1	21	292
37	444248.7.dec	3339085H1	21	298
37	444248.7.dec	4400849H1	21	217
37	444248.7.dec	1820977H1	21	321
37	444248.7.dec	3979337H1	22	320
37	444248.7.dec	1558436H1	26	274
37	444248.7.dec	2897306H1	28	334
37	444248.7.dec	768768H1	31	312
37	444248.7.dec	4577849H1	31	320

Table 4

37	444248.7.dec	1820284H1	31	320
37	444248.7.dec	2463163T6	49	504
37	444248.7.dec	5433096H1	89	342
37	444248.7.dec	1692729H1	156	366
37	444248.7.dec	4577774H1	179	274
37	444248.7.dec	5070606H1	393	655
37	444248.7.dec	3798947H1	14	311
37	444248.7.dec	1798841H1	47	293
37	444248.7.dec	4301418H1	19	284
37	444248.7.dec	4301419H1	19	281
37	444248.7.dec	3115509H1	18	129
38	346599.9.dec	3863294H1	1	253
38	346599.9.dec	3746375H1	1	261
38	346599.9.dec	2514968F6	6	423
38	346599.9.dec	2514968H1	6	168
38	346599.9.dec	2308505H1	17	282
38	346599.9.dec	2308637H1	17	253
38	346599.9.dec	3863323H1	21	284
38	346599.9.dec	866960H1	23	277
38	346599.9.dec	2561387H1	22	289
38	346599.9.dec	2523135H1	30	276
38	346599.9.dec	2518183H1	35	285
38	346599.9.dec	5027445H1	54	261
38	346599.9.dec	4155177H1	73	338
38	346599.9.dec	2561908H1	123	400
38	346599.9.dec	5020830H1	129	402
38	346599.9.dec	2962428H1	130	392
38	346599.9.dec	g4891117	144	397
38	346599.9.dec	g5554144	174	385
38	346599.9.dec	5156541H1	180	428
38	346599.9.dec	1490922H1	197	417
38	346599.9.dec	2316064H1	208	472
38	346599.9.dec	g922819	212	418
38	346599.9.dec	374753H1	216	423
38	346599.9.dec	3424858H1	228	499
38	346599.9.dec	g2968918	226	418
38	346599.9.dec	g2985496	249	418
38	346599.9.dec	g1063879	264	477
39	480344.2.dec	180805H1	1	195
39	480344.2.dec	065943H1	2	232
39	480344.2.dec	064251H1	31	213
39	480344.2.dec	071220H1	36	236
39	480344.2.dec	178296R6	37	272
39	480344.2.dec	g190646	53	1555
39	480344.2.dec	071770H1	61	290
39	480344.2.dec	g848952	459	801
39	480344.2.dec	g850712	476	738
39	480344.2.dec	g853560	509	839
39	480344.2.dec	g748042	511	712
39	480344.2.dec	g1443831	525	745
39	480344.2.dec	g848374	526	806
39	480344.2.dec	g611543	705	1064
39	480344.2.dec	062174H1	746	947
39	480344.2.dec	063483H1	746	940
39	480344.2.dec	063548H1	747	952
39	480344.2.dec	g839495	882	1094
39	480344.2.dec	g840023	1252	1556
39	480344.2.dec	g850541	1282	1556
39	480344.2.dec	g650883	1350	1553
39	480344.2.dec	g651032	1396	1553
40	411396.24.dec	3469388H1	959	1205
40	411396.24.dec	4032662H1	973	1232
40	411396.24.dec	2265224H1	1000	1236
40	411396.24.dec	g1527442	1006	1429
40	411396.24.dec	4583720H1	1035	1331
40	411396.24.dec	4147459H1	1050	1276
40	411396.24.dec	4548896T1	1053	1502
40	411396.24.dec	483899T6	1058	1514
40	411396.24.dec	4549096T1	1060	1500
40	411396.24.dec	1717178H1	1089	1336
40	411396.24.dec	g3645294	1094	1538
40	411396.24.dec	g4853243	1097	1538
40	411396.24.dec	2291135T6	1097	1501
40	411396.24.dec	g4649467	1126	1540
40	411396.24.dec	g4195074	1132	1541
40	411396.24.dec	2486118H1	1140	1374
40	411396.24.dec	g2881577	1155	1538
40	411396.24.dec	g2401496	1163	1540
40	411396.24.dec	690555H1	1167	1259
40	411396.24.dec	g2179339	1181	1541
40	411396.24.dec	2611377H1	1184	1423
40	411396.24.dec	5337142H1	1184	1440
40	411396.24.dec	1698746H1	1189	1386
40	411396.24.dec	2563483H1	1203	1467
40	411396.24.dec	g1891890	1233	1541
40	411396.24.dec	g3734944	1235	1538
40	411396.24.dec	715929H1	1237	1455
40	411396.24.dec	5580235H2	1242	1505
40	411396.24.dec	854921H1	1246	1508
40	411396.24.dec	g2186094	1247	1542
40	411396.24.dec	g1550426	1274	1538
40	411396.24.dec	g1203733	1277	1539
40	411396.24.dec	g2016376	1287	1538
40	411396.24.dec	702514H1	1302	1540
40	411396.24.dec	g2211872	1321	1546
40	411396.24.dec	2753527H1	1342	1544
40	411396.24.dec	g1203730	1391	1539
40	411396.24.dec	1326642H1	1397	1589
40	411396.24.dec	g5445022	1403	1605
40	411396.24.dec	3778081H1	1410	1538
40	411396.24.dec	g3002301	1444	1538
40	411396.24.dec	g4125232	1471	1538
40	411396.24.dec	1640624H1	1499	1687
40	411396.24.dec	1640663F6	1499	1687
40	411396.24.dec	4588787H1	1499	1690
40	411396.24.dec	1640663H1	1498	1687
40	411396.24.dec	721969H1	1499	1613
40	411396.24.dec	g2344373	1	388
40	411396.24.dec	4305707H1	1	285
40	411396.24.dec	2500749H1	32	285
40	411396.24.dec	4107921H1	45	240
40	411396.24.dec	4529582H1	46	300
40	411396.24.dec	g2033066	47	345
40	411396.24.dec	4198728H1	46	344
40	411396.24.dec	4298375H1	46	273
40	411396.24.dec	2265581H1	46	270
40	411396.24.dec	g1971997	46	294
40	411396.24.dec	2847731H1	47	302
40	411396.24.dec	213859H1	48	199
40	411396.24.dec	3246963H1	49	300
40	411396.24.dec	4080908H1	50	328
40	411396.24.dec	749419H1	52	300
40	411396.24.dec	6027207H1	52	343
40	411396.24.dec	2076551H1	54	263
40	411396.24.dec	g1390868	67	384
40	411396.24.dec	g2955514	69	440
40	411396.24.dec	g4268541	70	434
40	411396.24.dec	2908517H1	79	270
40	411396.24.dec	g2197932	78	424
40	411396.24.dec	g5636493	78	387
40	411396.24.dec	g5176779	81	393
40	411396.24.dec	g4892654	83	388
40	411396.24.dec	g3429293	88	431
40	411396.24.dec	g2198197	89	390

Table 4

40	411396.24.dec	g1784744	100	404
40	411396.24.dec	g1390758	103	376
40	411396.24.dec	6518113H1	108	634
40	411396.24.dec	2685370H1	131	374
40	411396.24.dec	g3149351	136	390
40	411396.24.dec	3601094H1	138	383
40	411396.24.dec	g3149496	136	388
40	411396.24.dec	3693617H1	182	458
40	411396.24.dec	5292656H2	206	376
40	411396.24.dec	4743230H1	209	390
40	411396.24.dec	g3069995	216	390
40	411396.24.dec	3143092H1	233	432
40	411396.24.dec	4369528H1	251	511
40	411396.24.dec	4335203H1	278	568
40	411396.24.dec	1871893H1	280	537
40	411396.24.dec	g2186404	287	666
40	411396.24.dec	g2184660	287	665
40	411396.24.dec	1947248H1	306	548
40	411396.24.dec	4643925H1	341	608
40	411396.24.dec	g1400216	348	424
40	411396.24.dec	2991447H1	485	793
40	411396.24.dec	g2930061	485	954
40	411396.24.dec	174444H1	541	753
40	411396.24.dec	174444R6	541	967
40	411396.24.dec	173477H1	541	733
40	411396.24.dec	4717029H1	564	805
40	411396.24.dec	2053919H1	570	827
40	411396.24.dec	1565945H1	571	777
40	411396.24.dec	3436125H1	587	814
40	411396.24.dec	4057202H1	588	859
40	411396.24.dec	5016627H1	594	876
40	411396.24.dec	1007141H1	602	866
40	411396.24.dec	5594568H1	608	843
40	411396.24.dec	6523363H1	617	1131
40	411396.24.dec	066953H1	636	821
40	411396.24.dec	6559965H1	637	1204
40	411396.24.dec	2904638H1	676	965
40	411396.24.dec	g1891889	679	951
40	411396.24.dec	1689134H1	737	976
40	411396.24.dec	5946816H1	809	1086
40	411396.24.dec	5550984H1	823	1043
40	411396.24.dec	2428835H1	843	1068
40	411396.24.dec	6408161H1	872	1145
40	411396.24.dec	g1238949	917	1197
40	411396.24.dec	g1238951	917	1126
40	411396.24.dec	6345172H1	923	1224
40	411396.24.dec	2291135R6	924	1299
40	411396.24.dec	2291135H1	924	1145
40	411396.24.dec	3716726H1	933	1247
40	411396.24.dec	161091H1	943	1140
40	411396.24.dec	5210085H1	951	1166
41	302819.4.dec	4101941H1	1	186
41	302819.4.dec	g4107114	21	1636
41	302819.4.dec	g4589481	50	3333
41	302819.4.dec	6061022H1	218	755
41	302819.4.dec	5481035H1	281	557
41	302819.4.dec	5481071H1	281	553
41	302819.4.dec	5478467H1	281	522
41	302819.4.dec	5476596H1	281	512
41	302819.4.dec	5481219H1	281	450
41	302819.4.dec	5692922H1	411	577
41	302819.4.dec	5091536H1	826	909
41	302819.4.dec	5093136H1	825	1088
41	302819.4.dec	4710301H1	856	1147
41	302819.4.dec	3330968H1	938	1192
41	302819.4.dec	6366367H1	954	1220
41	302819.4.dec	5844722H1	970	1252
41	302819.4.dec	2864086F6	1037	1444
41	302819.4.dec	2864086H1	1037	1322
41	302819.4.dec	g2835403	1364	1587
41	302819.4.dec	3944612F6	1376	1887
41	302819.4.dec	3944612H1	1376	1654
41	302819.4.dec	4311375F6	1414	1852
41	302819.4.dec	4311375H1	1414	1737
41	302819.4.dec	1229839H1	1577	1800
41	302819.4.dec	5497516H1	1627	1809
41	302819.4.dec	4178395H1	1670	1933
41	302819.4.dec	g575006	1833	2061
41	302819.4.dec	6382656H1	1834	2140
41	302819.4.dec	2152931H1	1941	2197
41	302819.4.dec	g791921	1957	2224
41	302819.4.dec	4785922H1	1958	2159
41	302819.4.dec	g953672	1966	2287
41	302819.4.dec	g1987264	1968	2265
41	302819.4.dec	5449040H1	2016	2260
41	302819.4.dec	5449083H1	2016	2294
41	302819.4.dec	4017288F6	2099	2454
41	302819.4.dec	4017288H1	2099	2257
41	302819.4.dec	648666H1	2106	2332
41	302819.4.dec	1614398H1	2139	2315
41	302819.4.dec	4244096F8	2141	2441
41	302819.4.dec	4754748H1	2165	2447
41	302819.4.dec	5268831H1	2194	2380
41	302819.4.dec	5857347H1	2203	2468
41	302819.4.dec	5835683H1	2204	2369
41	302819.4.dec	4330775H1	2205	2459
41	302819.4.dec	1288189F6	2275	2788
41	302819.4.dec	1288189H1	2275	2523
41	302819.4.dec	g1626001	2286	2647
41	302819.4.dec	5113638H1	2298	2483
41	302819.4.dec	g991068	2299	2451
41	302819.4.dec	5404686H1	2431	2650
41	302819.4.dec	2705579H1	2439	2713
41	302819.4.dec	4690513H1	2481	2679
41	302819.4.dec	1848103H1	2539	2776
41	302819.4.dec	4180730H1	2557	2744
41	302819.4.dec	6409441H1	2559	3089
41	302819.4.dec	2569213H1	2631	2873
41	302819.4.dec	4145445H1	2641	2924
41	302819.4.dec	6269094H1	2664	3208
41	302819.4.dec	3944612T6	2688	3284
41	302819.4.dec	g1885415	2709	3137
41	302819.4.dec	g1295339	2731	3182
41	302819.4.dec	1288189T6	2747	3292
41	302819.4.dec	5845876H1	2757	2850
41	302819.4.dec	3762741H1	2773	3061
41	302819.4.dec	2426329H1	2777	3006
41	302819.4.dec	4017288T6	2797	3294
41	302819.4.dec	4310250H1	2803	3112
41	302819.4.dec	4310267H1	2803	3114
41	302819.4.dec	4942836H1	2806	3077
41	302819.4.dec	4203668H1	2812	2967
41	302819.4.dec	6296936H1	2850	3171
41	302819.4.dec	1742377H1	2853	3141
41	302819.4.dec	4311375T6	2858	3290
41	302819.4.dec	g3154601	2859	3332
41	302819.4.dec	5478457H1	2866	3088
41	302819.4.dec	5482073H1	2867	3089
41	302819.4.dec	5482223H1	2867	3094
41	302819.4.dec	5480273H1	2867	3040
41	302819.4.dec	5480023H1	2867	2957
41	302819.4.dec	g4373364	2892	3335
41	302819.4.dec	g3411895	2897	3331
41	302819.4.dec	2151761H1	2904	3168

Table 4

41	302819.4.dec	2157650F6	2912	3333
41	302819.4.dec	2157650H1	2912	3026
41	302819.4.dec	5408984H1	2915	3123
41	302819.4.dec	2312364H1	2925	3005
41	302819.4.dec	g1625899	2955	3332
41	302819.4.dec	g3400238	2954	3343
41	302819.4.dec	g4687972	3018	3337
41	302819.4.dec	1940575H1	3026	3227
41	302819.4.dec	2328673H1	3039	3265
41	302819.4.dec	g4300411	3043	3335
41	302819.4.dec	g4267943	3046	3336
41	302819.4.dec	g825048	3051	3341
41	302819.4.dec	g991036	3052	3331
41	302819.4.dec	g567561	3097	3334
41	302819.4.dec	g1898761	3121	3336
41	302819.4.dec	g953400	3215	3338
41	302819.4.dec	1712751F6	3235	3334
41	302819.4.dec	1712751H1	3235	3334
41	302819.4.dec	1712751T6	3239	3296
41	302819.4.dec	2107049H1	3257	3334
41	302819.4.dec	g4532014	2983	3333
41	302819.4.dec	5839592H1	2990	3212
41	302819.4.dec	g4685396	3018	3337
41	302819.4.dec	g4299064	2964	3333
41	302819.4.dec	g4599081	2965	3335
41	302819.4.dec	g1265092	2965	3331
41	302819.4.dec	240555H1	2977	3157
42	238734.2.dec	g2307091	1	691
42	238734.2.dec	6507926H1	1	352
42	238734.2.dec	4447563H1	19	290
42	238734.2.dec	2027993H1	168	440
42	238734.2.dec	2027993R6	168	644
42	238734.2.dec	6075427H1	277	593
42	238734.2.dec	1403261H1	544	797
42	238734.2.dec	1403261F6	544	930
42	238734.2.dec	6454693H1	693	1320
42	238734.2.dec	6512287H1	1018	1563
42	238734.2.dec	5868348H1	1160	1439
42	238734.2.dec	5868348F6	1159	1660
42	238734.2.dec	902143R1	1458	1956
42	238734.2.dec	902143H1	1458	1736
42	238734.2.dec	1403261T6	1643	2240
42	238734.2.dec	531505T6	1705	2112
42	238734.2.dec	1511070H1	1830	2037
42	238734.2.dec	1511070F6	1830	2183
42	238734.2.dec	2569110H1	1893	2154
42	238734.2.dec	2568849H1	1893	2154
42	238734.2.dec	6260538H1	1963	2248
43	399525.3.dec	6120694H1	754	1295
43	399525.3.dec	2468280H1	710	947
43	399525.3.dec	4844519H1	1	269
43	399525.3.dec	3747370H1	37	337
43	399525.3.dec	341021H1	59	272
43	399525.3.dec	5983547H1	78	335
43	399525.3.dec	5522163H1	88	326
43	399525.3.dec	492858H1	858	1088
43	399525.3.dec	2928668F6	877	1159
43	399525.3.dec	2928668H1	878	1163
43	399525.3.dec	4289136H1	879	1140
43	399525.3.dec	5544612H2	893	970
43	399525.3.dec	405758H1	900	1121
43	399525.3.dec	g1685821	910	1234
43	399525.3.dec	3034576F6	950	1476
43	399525.3.dec	3034576F7	950	1418
43	399525.3.dec	3034576H1	951	1250
43	399525.3.dec	6157370H1	985	1233
43	399525.3.dec	6588995H1	1047	1558
43	399525.3.dec	180563R1	680	1157
43	399525.3.dec	180563H1	680	997
43	399525.3.dec	180563R6	680	1075
43	399525.3.dec	2009268H1	1284	1486
43	399525.3.dec	1629941H1	1293	1491
43	399525.3.dec	180563T6	1341	1687
43	399525.3.dec	5469050H1	1371	1623
43	399525.3.dec	5469049H1	1371	1531
43	399525.3.dec	5674214H1	1077	1344
43	399525.3.dec	g828577	1126	1362
43	399525.3.dec	180563F1	1185	1723
43	399525.3.dec	1267377T6	1250	1684
43	399525.3.dec	1267377F6	102	584
43	399525.3.dec	1267377F1	102	515
43	399525.3.dec	g2358795	127	184
43	399525.3.dec	5533757H1	452	689
43	399525.3.dec	5521485H1	499	718
43	399525.3.dec	5624724H1	519	815
43	399525.3.dec	1267377H1	102	361
43	399525.3.dec	5173655H1	651	908
44	222795.6.dec	g5231568	1	380
44	222795.6.dec	g4438873	1	420
44	222795.6.dec	6478906H1	1	373
44	222795.6.dec	g4888931	8	353
44	222795.6.dec	g5178893	8	400
44	222795.6.dec	g4301971	8	432
44	222795.6.dec	g4436204	8	328
44	222795.6.dec	g3401868	8	316
44	222795.6.dec	g4196406	8	271
44	222795.6.dec	3404674H1	17	79
44	222795.6.dec	3595184H1	28	317
44	222795.6.dec	1616015H1	62	278
44	222795.6.dec	1616788F6	62	384
44	222795.6.dec	2642562H1	85	331
44	222795.6.dec	2642562F6	85	248
44	222795.6.dec	3935234H1	146	420
44	222795.6.dec	5862138H1	160	420
44	222795.6.dec	5636483H1	183	432
44	222795.6.dec	5517092H1	182	390
44	222795.6.dec	6404623H1	395	606
44	222795.6.dec	5349471F6	186	639
44	222795.6.dec	5349471H1	186	436
44	222795.6.dec	6323776H1	372	571
44	222795.6.dec	3748145H1	378	622
44	222795.6.dec	6552507H1	590	701
44	222795.6.dec	6564675H1	592	779
44	222795.6.dec	6181144H1	625	910
44	222795.6.dec	3519117H1	705	976
44	222795.6.dec	6429178H1	726	877
44	222795.6.dec	3774768H1	893	1190
44	222795.6.dec	2214563H1	1114	1383
45	410628.5.dec	5469732H1	1	256
45	410628.5.dec	180125H1	2	220
45	410628.5.dec	g2008865	154	461
45	410628.5.dec	3364980H1	185	440
45	410628.5.dec	5912578H1	239	513
45	410628.5.dec	2829339F6	378	776
45	410628.5.dec	2829339H1	378	642
45	410628.5.dec	3807945H1	389	692
45	410628.5.dec	4008525H1	639	896
45	410628.5.dec	1852093F6	707	1214
45	410628.5.dec	1852093H1	707	974
45	410628.5.dec	2068781H1	727	1017
45	410628.5.dec	2131281H1	727	959
45	410628.5.dec	3483874H1	749	1023
45	410628.5.dec	1956841H1	759	1021
45	410628.5.dec	2928243H1	778	1037

Table 4

45	410628.5.dec	3893475H1	908	1148
45	410628.5.dec	077976H1	909	1059
45	410628.5.dec	2187402H1	927	1197
45	410628.5.dec	g1639418	934	1256
45	410628.5.dec	1910319H1	955	1197
45	410628.5.dec	2433701H1	1023	1250
45	410628.5.dec	1688079H1	1048	1249
45	410628.5.dec	2928651H1	1050	1142
45	410628.5.dec	5856935H1	1088	1381
45	410628.5.dec	6045234H1	1118	1591
45	410628.5.dec	6324874H1	1118	1176
45	410628.5.dec	g1638026	1130	1432
45	410628.5.dec	1907874H1	1152	1418
45	410628.5.dec	1964088R6	1200	1575
45	410628.5.dec	1964088H1	1200	1470
45	410628.5.dec	1352433H1	1201	1414
45	410628.5.dec	6045234J1	1205	1805
45	410628.5.dec	3752470H1	1214	1507
45	410628.5.dec	4720194H1	1231	1485
45	410628.5.dec	2829339T6	1238	1808
45	410628.5.dec	591385H1	1269	1495
45	410628.5.dec	3766513H1	1286	1580
45	410628.5.dec	2674849H1	1347	1596
45	410628.5.dec	3266918H1	1373	1653
45	410628.5.dec	g5232075	1373	1840
45	410628.5.dec	3412689H1	1374	1617
45	410628.5.dec	4502789H1	1377	1571
45	410628.5.dec	3962818H1	1378	1675
45	410628.5.dec	g2322969	1399	1831
45	410628.5.dec	g2432892	1455	1829
45	410628.5.dec	1964088T6	1485	1822
45	410628.5.dec	g4734424	1491	1942
45	410628.5.dec	1710011T6	1493	1815
45	410628.5.dec	g1955137	1511	1816
45	410628.5.dec	2604776F6	1522	2027
45	410628.5.dec	2604776H1	1522	1763
45	410628.5.dec	5636411H1	1523	1783
45	410628.5.dec	g2736627	1555	1948
45	410628.5.dec	g5632819	1568	1884
45	410628.5.dec	3738912H1	1574	1881
45	410628.5.dec	g4331385	1574	1859
45	410628.5.dec	g2002540	1592	1837
45	410628.5.dec	g2255929	1638	1837
45	410628.5.dec	g4310985	1641	2104
45	410628.5.dec	g1955138	1643	1883
45	410628.5.dec	4085875H1	1679	1943
45	410628.5.dec	g4703429	1840	2283
46	053649.6.dec	g2140414	4715	5138
46	053649.6.dec	g2752467	4717	5141
46	053649.6.dec	g3738044	4718	5139
46	053649.6.dec	4823575H1	4717	4978
46	053649.6.dec	6158080H1	4721	4829
46	053649.6.dec	g4607123	4728	5134
46	053649.6.dec	3535641H1	4740	5025
46	053649.6.dec	604476H1	4749	4991
46	053649.6.dec	607312H1	4750	4997
46	053649.6.dec	2865773H1	4777	5022
46	053649.6.dec	g2877086	4781	5141
46	053649.6.dec	1562789T6	4780	5129
46	053649.6.dec	1399654H1	4786	5034
46	053649.6.dec	g1957074	4788	5061
46	053649.6.dec	3039382H1	4795	5050
46	053649.6.dec	g4329155	4800	5133
46	053649.6.dec	3116891H1	4813	5054
46	053649.6.dec	2351206H1	4819	5029
46	053649.6.dec	4593993H1	4835	5096
46	053649.6.dec	4618056H1	4835	5084
46	053649.6.dec	2907550H1	4841	5144
46	053649.6.dec	6349673H2	4841	5135
46	053649.6.dec	3933835H1	4934	5204
46	053649.6.dec	3685046H1	4934	5172
46	053649.6.dec	4312063H1	4955	5233
46	053649.6.dec	1582279H1	4957	5132
46	053649.6.dec	g3988652	4982	5454
46	053649.6.dec	795706H1	4990	5228
46	053649.6.dec	1871289T6	5005	5412
46	053649.6.dec	4433271H1	5023	5281
46	053649.6.dec	1947703H1	5099	5298
46	053649.6.dec	g4763477	5110	5454
46	053649.6.dec	1876550H1	5134	5420
46	053649.6.dec	2427603H1	5155	5410
46	053649.6.dec	g3848344	5168	5454
46	053649.6.dec	5274403H1	5182	5436
46	053649.6.dec	2441651H1	5200	5424
46	053649.6.dec	454016R6	5209	5689
46	053649.6.dec	454016H1	5209	5432
46	053649.6.dec	3975767H1	5228	5505
46	053649.6.dec	g5526998	5242	5456
46	053649.6.dec	2777135H1	5244	5456
46	053649.6.dec	g1266554	5245	5526
46	053649.6.dec	6209668H1	5299	5610
46	053649.6.dec	282574H1	5302	5453
46	053649.6.dec	528280H1	5344	5630
46	053649.6.dec	g1623674	5351	5653
46	053649.6.dec	g2023447	5386	5614
46	053649.6.dec	4996368H1	5418	5688
46	053649.6.dec	4873622H1	5441	5700
46	053649.6.dec	1918585H1	5462	5730
46	053649.6.dec	394998R6	5483	5942
46	053649.6.dec	2608003H1	5528	5778
46	053649.6.dec	2869213H1	5536	5749
46	053649.6.dec	2846562H1	5536	5809
46	053649.6.dec	3549988H1	5536	5775
46	053649.6.dec	2878203H1	5538	5804
46	053649.6.dec	038436H1	5551	5798
46	053649.6.dec	2859240H1	5556	5812
46	053649.6.dec	447581H1	5563	5777
46	053649.6.dec	6543240H1	5619	6031
46	053649.6.dec	1924182R6	5631	5923
46	053649.6.dec	1924182H1	5631	5853
46	053649.6.dec	454016T6	5637	6309
46	053649.6.dec	2857928H1	5651	5916
46	053649.6.dec	6518276H1	5654	6091
46	053649.6.dec	3093841H1	5656	5933
46	053649.6.dec	g2155719	5667	5875
46	053649.6.dec	1924182T6	5689	6258
46	053649.6.dec	3116771H1	5729	6000
46	053649.6.dec	3510740T6	5789	6255
46	053649.6.dec	2357646F6	5787	6264
46	053649.6.dec	2357646H1	5787	6011
46	053649.6.dec	018607H1	5789	6079
46	053649.6.dec	017537H1	5789	6050
46	053649.6.dec	015937H1	5789	6038
46	053649.6.dec	016285H1	5789	6052
46	053649.6.dec	621377R6	5821	6295
46	053649.6.dec	621377T6	5821	6258
46	053649.6.dec	621377H1	5821	6083
46	053649.6.dec	g2197952	5853	6298
46	053649.6.dec	g1859838	5860	6289
46	053649.6.dec	g4982575	5873	6297
46	053649.6.dec	g5632069	5874	6303
46	053649.6.dec	3331637H1	5875	6123
46	053649.6.dec	g3917437	5878	6304
46	053649.6.dec	3320110H1	5881	6166

Table 4

46	053649.6.dec	470544H1	5881	6131
46	053649.6.dec	g4260778	5892	6346
46	053649.6.dec	061289H1	5901	6055
46	053649.6.dec	g5526193	5903	6303
46	053649.6.dec	3200859H1	5937	6216
46	053649.6.dec	2463691H1	5960	6177
46	053649.6.dec	2378781H1	5963	6184
46	053649.6.dec	849937H1	6881	7000
46	053649.6.dec	6396030H1	6458	6756
46	053649.6.dec	g3094377	6488	6953
46	053649.6.dec	g4606923	6500	6957
46	053649.6.dec	g751556	6503	6702
46	053649.6.dec	g4291182	6509	6959
46	053649.6.dec	g3849739	6509	6957
46	053649.6.dec	g5671130	6517	6968
46	053649.6.dec	g3764849	6530	6954
46	053649.6.dec	2230287H1	6551	6799
46	053649.6.dec	g1218106	6563	6953
46	053649.6.dec	g3756320	6573	6959
46	053649.6.dec	g2188518	6591	6910
46	053649.6.dec	4000865H1	6644	6917
46	053649.6.dec	g2270783	6663	6971
46	053649.6.dec	5709816H1	6073	6342
46	053649.6.dec	2469521H1	6085	6306
46	053649.6.dec	4256123H1	5968	6240
46	053649.6.dec	4245703H1	5978	6255
46	053649.6.dec	g5446227	5984	6348
46	053649.6.dec	4091718H1	6032	6256
46	053649.6.dec	2357646T6	6065	6299
46	053649.6.dec	g1778032	1	6659
46	053649.6.dec	1271488H1	270	501
46	053649.6.dec	6177281H1	282	549
46	053649.6.dec	4535853H1	1492	1746
46	053649.6.dec	2998346H1	1576	1847
46	053649.6.dec	183990H1	1784	1957
46	053649.6.dec	2416184H1	1894	2137
46	053649.6.dec	5537614H1	2185	2376
46	053649.6.dec	g2817443	2299	2770
46	053649.6.dec	2015073H1	2315	2562
46	053649.6.dec	g3644396	2346	2771
46	053649.6.dec	g4270510	2435	2770
46	053649.6.dec	5080263H1	2919	3138
46	053649.6.dec	4872695H1	2991	3250
46	053649.6.dec	4398050H1	3001	3257
46	053649.6.dec	2723988H1	3048	3289
46	053649.6.dec	2836887H1	3186	3441
46	053649.6.dec	3901067H1	3335	3594
46	053649.6.dec	3510740F6	3517	3957
46	053649.6.dec	3510740H1	3517	3786
46	053649.6.dec	3340558H1	3636	3901
46	053649.6.dec	4347614H1	3688	3944
46	053649.6.dec	1562789F6	3799	4220
46	053649.6.dec	1562781H1	3799	4019
46	053649.6.dec	1562789H1	3799	4021
46	053649.6.dec	2431585H1	3818	4046
46	053649.6.dec	5408836H1	3906	4164
46	053649.6.dec	4350359H1	3911	4166
46	053649.6.dec	881810H1	3939	4180
46	053649.6.dec	6408412H1	3945	4490
46	053649.6.dec	6454776H1	3990	4455
46	053649.6.dec	1708247H1	4017	4242
46	053649.6.dec	1376453H1	4018	4238
46	053649.6.dec	2917695H1	4120	4396
46	053649.6.dec	4913391H1	4123	4316
46	053649.6.dec	2433842H1	4141	4349
46	053649.6.dec	6477331H1	4227	4751
46	053649.6.dec	2285180T6	4466	5094
46	053649.6.dec	2285180H1	4464	4717
46	053649.6.dec	2285180R6	4465	4934
46	053649.6.dec	4381173H1	4489	4762
46	053649.6.dec	3071901H1	4490	4775
46	053649.6.dec	2246853H1	4497	4749
46	053649.6.dec	2519418H1	4503	4759
46	053649.6.dec	2589642H1	4503	4747
46	053649.6.dec	1684996H1	4503	4687
46	053649.6.dec	6109482H1	4561	4852
46	053649.6.dec	1509877H1	4561	4755
46	053649.6.dec	5091092H1	4588	4843
46	053649.6.dec	5074194H1	4621	4900
46	053649.6.dec	3770734H1	4644	4927
46	053649.6.dec	655534H1	4649	4876
46	053649.6.dec	3865590H1	4643	4839
46	053649.6.dec	2751219H1	6404	6675
46	053649.6.dec	1463185H1	6085	6262
46	053649.6.dec	1463209T6	6085	6259
46	053649.6.dec	447899H1	6097	6164
46	053649.6.dec	394998T6	6121	6634
46	053649.6.dec	126467H1	6122	6390
46	053649.6.dec	2603006H1	6180	6456
46	053649.6.dec	582896H1	6194	6440
46	053649.6.dec	3630189H1	6199	6389
46	053649.6.dec	4629688H1	6205	6357
46	053649.6.dec	g4326882	6226	6674
46	053649.6.dec	g4852252	6234	6680
46	053649.6.dec	g4074077	6250	6679
46	053649.6.dec	4744510H1	6253	6495
46	053649.6.dec	2602237F6	6709	6953
46	053649.6.dec	2602237H1	6709	6980
46	053649.6.dec	2602237T6	6710	6915
46	053649.6.dec	505561H1	6772	6953
46	053649.6.dec	1463209R6	6085	6297
46	053649.6.dec	g3770766	6708	6962
47	221914.2.dec	2692351H1	66	317
47	221914.2.dec	3324937H1	40	301
47	221914.2.dec	1510086H1	42	260
47	221914.2.dec	1521573H1	47	236
47	221914.2.dec	3402411H1	65	235
47	221914.2.dec	2991821H1	205	426
47	221914.2.dec	3417004H1	240	480
47	221914.2.dec	3393041H1	275	543
47	221914.2.dec	g3405497	405	701
47	221914.2.dec	4515647H1	468	682
47	221914.2.dec	4121840H1	504	719
47	221914.2.dec	3422922H1	504	728
47	221914.2.dec	4514527H1	516	761
47	221914.2.dec	1957812H1	608	883
47	221914.2.dec	2137153F6	1	168
47	221914.2.dec	2137153H1	1	236
47	221914.2.dec	3615140H1	6	287
47	221914.2.dec	2017382H1	17	145
47	221914.2.dec	3508367H1	17	116
47	221914.2.dec	3748348H1	17	188
47	221914.2.dec	1491036H1	37	210
47	221914.2.dec	2520837H1	38	265
47	221914.2.dec	1957812F6	608	1033
47	221914.2.dec	1871603H1	706	831
47	221914.2.dec	3939407H1	821	925
48	347748.2.dec	3272638H1	1	235
48	347748.2.dec	3568428H1	5	318
48	347748.2.dec	1591195H1	17	220
48	347748.2.dec	1591381H1	17	242
48	347748.2.dec	3108209H1	18	112
48	347748.2.dec	6369107H1	24	471
48	347748.2.dec	3436985H1	25	112

Table 4

48	347748.2.dec	3472447H1	31	267
48	347748.2.dec	3271083H1	171	402
48	347748.2.dec	4181728H1	195	281
48	347748.2.dec	6477761H1	229	407
48	347748.2.dec	g3778189	312	759
48	347748.2.dec	g3179263	312	497
48	347748.2.dec	g3050805	314	558
48	347748.2.dec	g3174659	315	812
48	347748.2.dec	512461H1	338	542
48	347748.2.dec	512461R6	338	686
48	347748.2.dec	446066H1	338	579
48	347748.2.dec	442400H1	339	579
48	347748.2.dec	3097735H1	484	712
48	347748.2.dec	3540123H1	509	787
48	347748.2.dec	3319530H1	576	637
48	347748.2.dec	g1970848	599	927
48	347748.2.dec	g1970843	599	872
48	347748.2.dec	g2000224	609	870
48	347748.2.dec	425094H1	803	951
48	347748.2.dec	424797H1	803	1010
48	347748.2.dec	428193H1	803	1019
48	347748.2.dec	2552119H1	853	1114
48	347748.2.dec	5511770H1	617	861
48	347748.2.dec	6489362H1	689	1258
48	347748.2.dec	4674740H1	690	990
48	347748.2.dec	1405304H1	972	1249
48	347748.2.dec	2868023H1	999	1231
48	347748.2.dec	g2011228	715	1019
48	347748.2.dec	4774949H1	727	871
48	347748.2.dec	5004188H1	791	1031
48	347748.2.dec	2687450H1	801	1060
48	347748.2.dec	428193R6	803	1166
48	347748.2.dec	424588H1	803	871
48	347748.2.dec	425651H1	803	1024
48	347748.2.dec	428193T6	1121	1733
48	347748.2.dec	5089180H1	1169	1430
48	347748.2.dec	2111317H1	1292	1552
49	401482.2.oct	3380414H1	141	264
49	401482.2.oct	3806831H1	141	260
49	401482.2.oct	3152624H1	140	323
49	401482.2.oct	6008631H1	140	311
49	401482.2.oct	1599727H1	140	304
49	401482.2.oct	4536938H1	140	258
49	401482.2.oct	3606772H1	140	252
49	401482.2.oct	4830281H1	141	230
49	401482.2.oct	1308766H1	140	294
49	401482.2.oct	2666290H1	140	250
49	401482.2.oct	2072576H1	140	304
49	401482.2.oct	4974839H1	140	304
49	401482.2.oct	3807429H1	141	304
49	401482.2.oct	2524335H1	140	311
49	401482.2.oct	1527079H1	140	261
49	401482.2.oct	137226H1	140	311
49	401482.2.oct	3081905H1	140	288
49	401482.2.oct	2286712H1	140	294
49	401482.2.oct	2189156H1	140	248
49	401482.2.oct	1550788H1	140	304
49	401482.2.oct	2736933H1	140	230
49	401482.2.oct	592827H1	140	268
49	401482.2.oct	2074671H1	140	301
49	401482.2.oct	6105031H1	140	255
49	401482.2.oct	4563727H1	140	311
49	401482.2.oct	2741386H1	140	266
49	401482.2.oct	3807627H1	140	265
49	401482.2.oct	2854386H1	140	237
49	401482.2.oct	4833902H1	140	277
49	401482.2.oct	540768H1	140	311
49	401482.2.oct	4363412H1	140	231
49	401482.2.oct	592882H1	140	262
49	401482.2.oct	4128816H1	140	306
49	401482.2.oct	5066972H1	141	237
49	401482.2.oct	6375187H1	140	221
49	401482.2.oct	4057141H1	140	268
49	401482.2.oct	368551H1	143	294
49	401482.2.oct	5262823H1	140	292
49	401482.2.oct	4008852H1	140	272
49	401482.2.oct	4563645H1	140	220
49	401482.2.oct	4982802H1	148	301
49	401482.2.oct	3490679H1	140	303
49	401482.2.oct	3142629H1	143	265
49	401482.2.oct	820429H1	142	238
49	401482.2.oct	1268873H1	140	304
49	401482.2.oct	2839681H2	140	269
49	401482.2.oct	3865664H1	141	257
49	401482.2.oct	4662861H1	141	207
49	401482.2.oct	1708280H1	136	250
49	401482.2.oct	g1983680	136	299
49	401482.2.oct	3897334H1	135	304
49	401482.2.oct	g1996315	135	323
49	401482.2.oct	4743463H1	135	277
49	401482.2.oct	3570680H1	135	274
49	401482.2.oct	3891485H1	129	293
49	401482.2.oct	983595H1	129	239
49	401482.2.oct	4956529H1	129	290
49	401482.2.oct	1681495H1	129	311
49	401482.2.oct	5376752H1	124	296
49	401482.2.oct	1308930H1	129	238
49	401482.2.oct	3881848H1	129	332
49	401482.2.oct	1643328H1	129	311
49	401482.2.oct	3927505H1	130	304
49	401482.2.oct	5389939H1	129	296
49	401482.2.oct	4612035H1	124	384
49	401482.2.oct	5687077H1	124	381
49	401482.2.oct	2378181H1	127	346
49	401482.2.oct	2457930H1	127	280
49	401482.2.oct	3889660H1	130	304
49	401482.2.oct	4460811H1	130	243
49	401482.2.oct	3878648H1	130	248
49	401482.2.oct	868503H1	129	311
49	401482.2.oct	1642356H1	129	332
49	401482.2.oct	2739322H1	129	311
49	401482.2.oct	2353257H1	129	281
49	401482.2.oct	5043438H1	146	271
49	401482.2.oct	1721132H1	129	311
49	401482.2.oct	194897H1	129	350
49	401482.2.oct	4528304H1	129	270
49	401482.2.oct	2859113H1	129	332
49	401482.2.oct	3777804H1	130	269
49	401482.2.oct	2777981H1	129	380
49	401482.2.oct	1480087H1	129	311
49	401482.2.oct	814473H1	129	212
49	401482.2.oct	1375967H1	129	323
49	401482.2.oct	1556743H1	129	323
49	401482.2.oct	1912456H1	129	332
49	401482.2.oct	3861078H1	129	258
49	401482.2.oct	371153H1	129	304
49	401482.2.oct	373185H1	129	323
49	401482.2.oct	4058394H1	129	235
49	401482.2.oct	116195H1	129	299
49	401482.2.oct	5106028H1	131	232
49	401482.2.oct	4549024H1	130	304
49	401482.2.oct	586154H1	129	371
49	401482.2.oct	2073746H1	129	219
49	401482.2.oct	128113H1	131	245

Table 4

49	401482.2.oct	4585185H1	129	364
49	401482.2.oct	1892064H1	129	304
49	401482.2.oct	1625250H1	129	218
49	401482.2.oct	2357189H1	129	261
49	401482.2.oct	4630841H1	134	272
49	401482.2.oct	5699535H1	129	375
49	401482.2.oct	2071024H1	129	323
49	401482.2.oct	2808648H1	127	304
49	401482.2.oct	4632985H1	129	385
49	401482.2.oct	948410H1	129	311
49	401482.2.oct	2650195H1	129	311
49	401482.2.oct	1911720H1	129	282
49	401482.2.oct	5557203H1	129	303
49	401482.2.oct	5187021H1	129	280
49	401482.2.oct	4343951H1	129	282
49	401482.2.oct	g1734245	129	221
49	401482.2.oct	g1734234	129	221
49	401482.2.oct	4550125H1	130	392
49	401482.2.oct	2026970H1	149	204
49	401482.2.oct	3056876H1	129	339
49	401482.2.oct	4721629H1	130	247
49	401482.2.oct	4347191H1	128	302
49	401482.2.oct	5978251H1	130	180
49	401482.2.oct	4815016H1	130	311
49	401482.2.oct	3430533H1	129	337
49	401482.2.oct	1578109H1	129	347
49	401482.2.oct	4580668H1	129	274
49	401482.2.oct	4349130H1	129	330
49	401482.2.oct	1610424H1	129	304
49	401482.2.oct	3364209H1	129	260
49	401482.2.oct	6136479H1	130	271
49	401482.2.oct	3398472H1	130	239
49	401482.2.oct	3015102H1	129	223
49	401482.2.oct	5081859H1	129	299
49	401482.2.oct	4338871H1	129	284
49	401482.2.oct	4585911H1	130	264
49	401482.2.oct	113024H1	130	303
49	401482.2.oct	540069H1	136	200
49	401482.2.oct	6139403H1	130	332
49	401482.2.oct	2652958H1	130	255
49	401482.2.oct	4702083H1	130	234
49	401482.2.oct	3918683H1	132	289
49	401482.2.oct	4821911H1	129	280
49	401482.2.oct	4501456H1	129	323
49	401482.2.oct	1899608H1	129	260
49	401482.2.oct	1610410H1	129	311
49	401482.2.oct	3891265H1	144	251
49	401482.2.oct	4502830H1	143	270
49	401482.2.oct	2924159H1	141	243
49	401482.2.oct	2106528H1	141	285
49	401482.2.oct	1895746H1	141	293
49	401482.2.oct	1799893H1	141	223
49	401482.2.oct	3440365H1	141	311
49	401482.2.oct	697099H1	141	276
49	401482.2.oct	5220546H1	141	311
49	401482.2.oct	4640268H1	131	304
49	401482.2.oct	1591126H1	131	304
49	401482.2.oct	1591132H1	131	304
49	401482.2.oct	g1270001	133	205
49	401482.2.oct	4346815H1	131	244
49	401482.2.oct	3959778H2	132	323
49	401482.2.oct	117063H1	133	244
49	401482.2.oct	389507H1	131	235
49	401482.2.oct	2737221H1	132	304
49	401482.2.oct	5573958H1	130	344
49	401482.2.oct	3604159H1	130	280
49	401482.2.oct	6099064H1	130	295
49	401482.2.oct	g2325824	1	234
49	401482.2.oct	5794810H1	32	300
49	401482.2.oct	5792265H1	51	300
49	401482.2.oct	5947232H1	121	353
49	401482.2.oct	807770H1	122	224
49	401482.2.oct	5947296H1	122	223
49	401482.2.oct	3358464H1	128	419
49	401482.2.oct	g1614987	147	549
49	401482.2.oct	g1614885	235	579
49	401482.2.oct	2096459H1	132	288
49	401482.2.oct	5077509H1	132	311
49	401482.2.oct	3672962H1	132	267
49	401482.2.oct	2495269H1	133	292
49	401482.2.oct	5582685H1	133	299
49	401482.2.oct	2237565H1	133	231
49	401482.2.oct	4409210H1	133	283
49	401482.2.oct	4455694H1	133	323
49	401482.2.oct	082693H1	133	273
49	401482.2.oct	1738401H1	133	244
49	401482.2.oct	g1816100	133	293
49	401482.2.oct	1372579H1	133	237
49	401482.2.oct	g2005112	132	311
49	401482.2.oct	4379011H1	132	301
49	401482.2.oct	5162976H1	132	237
49	401482.2.oct	2518933H1	132	223
49	401482.2.oct	405083H1	132	266
49	401482.2.oct	2383796H1	132	301
49	401482.2.oct	4585939H1	132	293
49	401482.2.oct	g1439429	132	249
49	401482.2.oct	5556467H1	135	300
49	401482.2.oct	3117637H1	136	304
49	401482.2.oct	3230457H1	136	304
49	401482.2.oct	3153383H1	135	311
49	401482.2.oct	637896H1	143	376
50	274551.1.oct	g4325750	1	103
50	274551.1.oct	4290049F6	1	353
50	274551.1.oct	4290049H1	1	124
50	274551.1.oct	5493752H1	172	444
51	411408.20.dec	936827H1	525	638
51	411408.20.dec	2375133H1	443	614
51	411408.20.dec	2300942H1	492	621
51	411408.20.dec	5023109H1	442	622
51	411408.20.dec	4418917H1	174	410
51	411408.20.dec	3674792H1	393	749
51	411408.20.dec	2805943H1	393	756
51	411408.20.dec	1966865H1	391	720
51	411408.20.dec	4653403H1	393	734
51	411408.20.dec	4956215H1	393	718
51	411408.20.dec	4109951H1	393	726
51	411408.20.dec	2812018H1	393	719
51	411408.20.dec	402737H1	393	742
51	411408.20.dec	3770868H1	394	765
51	411408.20.dec	3838768H1	392	737
51	411408.20.dec	1403444H1	393	738
51	411408.20.dec	3667386H1	393	744
51	411408.20.dec	3153604H1	394	671
51	411408.20.dec	2992279H1	392	746
51	411408.20.dec	3746578H1	393	587
51	411408.20.dec	4767753H1	392	734
51	411408.20.dec	2943178H1	393	764
51	411408.20.dec	2586769H1	392	743
51	411408.20.dec	3160466H1	393	743
51	411408.20.dec	2832332H1	393	701
51	411408.20.dec	4912762H1	402	740
51	411408.20.dec	983356H1	395	758
51	411408.20.dec	5191120H1	392	701
51	411408.20.dec	3637826H1	394	742

Table 4

51	411408.20.dec	g2252026	396	814
51	411408.20.dec	6132793H1	392	724
51	411408.20 dec	2907546H1	395	782
51	411408.20.dec	785404H1	396	742
51	411408.20.dec	185321H1	397	613
51	411408.20.dec	389185H1	396	743
51	411408.20.dec	3534063H1	396	799
51	411408.20.dec	3996765H1	396	659
51	411408.20.dec	3053279H1	398	516
51	411408.20.dec	1807609H1	399	736
51	411408.20.dec	2523052H1	399	737
51	411408.20.dec	4977531H1	399	735
51	411408.20.dec	3858932H1	400	740
51	411408.20.dec	1845501H1	398	658
51	411408.20.dec	816386H1	399	746
51	411408.20.dec	4198843H1	399	743
51	411408.20.dec	4042101H1	398	724
51	411408.20.dec	3750944H1	400	758
51	411408.20.dec	937287H1	400	738
51	411408.20.dec	3810490H1	400	740
51	411408.20.dec	3114955H1	401	756
51	411408.20.dec	4566634H1	401	753
51	411408.20.dec	3705807H1	402	773
51	411408.20.dec	4066846H1	401	743
51	411408.20.dec	371959H1	403	562
51	411408.20.dec	4626333H1	403	736
51	411408.20.dec	4956823H1	403	742
51	411408.20.dec	3670548H1	406	742
51	411408.20.dec	3051835H1	403	768
51	411408.20.dec	029644H1	405	745
51	411408.20.dec	1535449H1	404	654
51	411408.20.dec	3592104H1	405	756
51	411408.20.dec	3993941H2	405	748
51	411408.20.dec	5028325H1	406	750
51	411408.20.dec	3808513H1	419	811
51	411408.20.dec	3076490H1	423	753
51	411408.20.dec	5020492H1	423	750
51	411408.20.dec	2318857H1	423	764
51	411408.20.dec	506742H1	424	565
51	411408.20.dec	3995849H1	423	768
51	411408.20.dec	4126641H1	427	781
51	411408.20.dec	3930274H1	430	700
51	411408.20.dec	2463303H1	436	756
51	411408.20.dec	3137131H1	436	781
51	411408.20.dec	767735H1	448	735
51	411408.20.dec	g2056448	461	951
51	411408.20.dec	744424H1	468	749
51	411408.20.dec	508365H1	470	746
51	411408.20.dec	1541976H1	527	801
51	411408.20.dec	2404134H1	530	791
51	411408.20.dec	1597375T6	704	861
51	411408.20.dec	5700996H1	385	736
51	411408.20.dec	2470451H1	385	716
51	411408.20.dec	4980959H1	385	717
51	411408.20.dec	2318026H1	386	713
51	411408.20.dec	4702372H1	385	705
51	411408.20.dec	6562862H1	392	830
51	411408.20.dec	2605436H1	386	704
51	411408.20.dec	3567254H1	386	650
51	411408.20.dec	4976438H1	386	712
51	411408.20.dec	1984353H1	386	724
51	411408.20.dec	5946551H1	386	746
51	411408.20.dec	764555H1	387	703
51	411408.20.dec	g1955984	387	714
51	411408.20.dec	736413R1	388	859
51	411408.20.dec	4327844H1	391	700
51	411408.20.dec	3617318H1	388	758
51	411408.20.dec	3477204H1	387	804
51	411408.20.dec	g1357803	390	1071
51	411408.20.dec	4946208H1	388	685
51	411408.20.dec	1576142H1	388	678
51	411408.20.dec	g2619527	389	792
51	411408.20.dec	743255H1	388	719
51	411408.20.dec	4958275H1	389	719
51	411408.20.dec	2552783H1	389	692
51	411408.20.dec	5098761H1	389	710
51	411408.20.dec	1478849H1	389	680
51	411408.20.dec	2856522H1	392	721
51	411408.20.dec	5687388H1	390	708
51	411408.20.dec	4523823H1	390	716
51	411408.20.dec	3490029H1	390	750
51	411408.20.dec	5046950H1	390	726
51	411408.20.dec	4586244H1	390	713
51	411408.20.dec	2459258H1	390	708
51	411408.20.dec	1858361H1	390	709
51	411408.20.dec	4416909H1	389	717
51	411408.20.dec	4523905H1	389	703
51	411408.20.dec	2760918H1	390	762
51	411408.20.dec	4385055H1	390	713
51	411408.20.dec	4853641H1	390	746
51	411408.20.dec	4819893H1	388	701
51	411408.20.dec	3918493H1	390	726
51	411408.20.dec	4367949H1	391	703
51	411408.20.dec	4525882H1	391	703
51	411408.20.dec	4154002H1	391	718
51	411408.20.dec	5671105H1	392	590
51	411408.20.dec	5574281H1	391	703
51	411408.20.dec	4981071H1	391	745
51	411408.20.dec	4895035H1	391	744
51	411408.20.dec	5122182H1	392	727
51	411408.20.dec	4329866H1	391	700
51	411408.20.dec	5199638H1	392	544
51	411408.20.dec	2548578H1	391	687
51	411408.20.dec	4730925H1	391	717
51	411408.20.dec	3495911H1	391	743
51	411408.20.dec	2116906H1	391	713
51	411408.20.dec	2555366H1	391	691
51	411408.20.dec	4544977H1	391	690
51	411408.20.dec	3373476H1	391	709
51	411408.20.dec	2966550H1	392	682
51	411408.20.dec	2763323H1	391	692
51	411408.20.dec	4874466H1	391	719
51	411408.20.dec	2548853H1	392	712
51	411408.20.dec	4841824H1	391	746
51	411408.20.dec	4953663H1	391	695
51	411408.20.dec	5115420H1	392	735
51	411408.20.dec	4845489H1	391	633
51	411408.20.dec	2684639H1	391	694
51	411408.20.dec	6376757H1	392	723
51	411408.20.dec	2606634H1	392	698
51	411408.20.dec	3298129H1	391	700
51	411408.20.dec	4767905H1	390	736
51	411408.20.dec	2256874H1	391	704
51	411408.20.dec	4982262H1	391	726
51	411408.20.dec	3662084H1	391	742
51	411408.20.dec	4843594H1	392	718
51	411408.20.dec	3675093H1	392	746
51	411408.20.dec	4385088H1	391	712
51	411408.20.dec	2548726H1	392	709
51	411408.20.dec	3351335H1	390	713
51	411408.20.dec	3442587H1	392	565
51	411408.20.dec	3995356H2	392	745
51	411408.20.dec	4653711H1	392	745
51	411408.20.dec	4977378H1	392	731

Table 4

51	411408.20.dec	3456074H1	392	711
51	411408.20.dec	4765640H1	392	710
51	411408.20.dec	2544077H1	392	743
51	411408.20.dec	5175221H1	392	546
51	411408.20.dec	2649975H1	393	709
51	411408.20.dec	780432H1	392	526
51	411408.20.dec	1613961H1	393	517
51	411408.20.dec	780667H1	392	734
51	411408.20.dec	4976638H1	391	723
51	411408.20.dec	4955591H1	392	735
51	411408.20.dec	4917657H1	392	735
51	411408.20.dec	2211455H1	393	714
51	411408.20.dec	4750777H1	392	737
51	411408.20.dec	4372262H1	392	729
51	411408.20.dec	2502217H1	392	698
51	411408.20.dec	4564914H1	392	695
51	411408.20.dec	4546001H1	392	754
51	411408.20.dec	4124159H1	392	729
51	411408.20.dec	3976845H1	392	613
51	411408.20.dec	4503808H1	390	713
51	411408.20.dec	3055191H1	391	743
51	411408.20.dec	4662503H1	392	703
51	411408.20.dec	2605825H1	392	736
51	411408.20.dec	1005043H1	392	720
51	411408.20.dec	2446394H1	393	674
51	411408.20.dec	4990021H1	392	726
51	411408.20.dec	4148690H1	392	729
51	411408.20.dec	3607084H1	392	663
51	411408.20.dec	5085183H1	391	704
51	411408.20.dec	2857082H1	392	711
51	411408.20.dec	2632563H1	392	734
51	411408.20.dec	4906727H2	392	759
51	411408.20.dec	2700833H1	392	658
51	411408.20.dec	2535528H1	392	657
51	411408.20.dec	3490780H1	392	759
51	411408.20.dec	3894336H1	392	761
51	411408.20.dec	3970513H1	392	758
51	411408.20.dec	3171791H1	392	618
51	411408.20.dec	1723460H1	392	611
51	411408.20.dec	3476891H1	392	807
51	411408.20.dec	4981057H1	392	749
51	411408.20.dec	4802806H1	392	749
51	411408.20.dec	4110394H1	392	588
51	411408.20.dec	3575464H1	392	565
51	411408.20.dec	1729387H1	1	113
51	411408.20.dec	3000408H1	5	303
51	411408.20.dec	5303401H1	18	112
51	411408.20.dec	3182425H1	123	458
51	411408.20.dec	3056336H2	126	448
51	411408.20.dec	3747433H1	130	439
51	411408.20.dec	3640626H1	132	448
51	411408.20.dec	4938579H1	135	447
51	411408.20.dec	3880456H1	140	439
51	411408.20.dec	4642677H1	144	448
51	411408.20.dec	4981352H1	144	448
51	411408.20.dec	4052414H1	147	459
51	411408.20.dec	3142667H1	151	449
51	411408.20.dec	4021007H1	155	448
51	411408.20.dec	4992340H1	161	448
51	411408.20.dec	5036067H1	164	452
51	411408.20.dec	5035975H1	167	451
51	411408.20.dec	5572423H1	195	448
51	411408.20.dec	5263066H1	322	432
51	411408.20.dec	3076106H1	351	711
51	411408.20.dec	2394983H1	354	623
51	411408.20.dec	6174661H1	361	719
51	411408.20.dec	2052284H1	361	677
51	411408.20.dec	2591832H1	367	654
51	411408.20.dec	2155019H1	361	448
51	411408.20.dec	1709953H1	373	663
51	411408.20.dec	4083858H1	373	712
51	411408.20.dec	2554967H1	374	663
51	411408.20.dec	3993314H1	374	743
51	411408.20.dec	4975109H1	373	724
51	411408.20.dec	646957H1	380	717
51	411408.20.dec	2150550H1	383	736
51	411408.20.dec	3179540H1	382	768
51	411408.20.dec	1970802H1	381	731
51	411408.20.dec	3737635H1	382	759
51	411408.20.dec	4521821H1	382	703
51	411408.20.dec	4556748H1	382	700
51	411408.20.dec	1798726H1	382	691
51	411408.20.dec	4145903H1	382	789
51	411408.20.dec	4150946H1	382	703
51	411408.20.dec	3118151H1	383	749
51	411408.20.dec	1973414H1	383	704
51	411408.20.dec	3621844H1	382	723
51	411408.20.dec	2156096H1	387	686
51	411408.20.dec	4150328H1	381	718
51	411408.20.dec	2806959H1	382	661
51	411408.20.dec	5059914H1	382	716
51	411408.20.dec	5053073H1	384	603
51	411408.20.dec	3898664H1	383	705
51	411408.20.dec	2668117H1	382	710
51	411408.20.dec	3023657H1	382	724
51	411408.20.dec	2551978H1	383	712
51	411408.20.dec	4710332H1	384	736
51	411408.20.dec	4138190H1	384	751
51	411408.20.dec	5684104H1	385	727
51	411408.20.dec	4797725H1	386	714
51	411408.20.dec	5669575H1	390	627
51	411408.20.dec	598827H1	442	552
51	411408.20.dec	891997H1	443	578
51	411408.20.dec	753453H1	491	588
51	411408.20.dec	2465958H1	483	593
51	411408.20.dec	4831218H1	444	579
51	411408.20.dec	598686H1	442	601
52	035973.1.dec	5401350H1	1	105
52	035973.1.dec	6057617H1	56	643
52	035973.1.dec	g3214092	406	782
52	035973.1.dec	3524102H1	479	779
53	456536.1.dec	g819467	922	1236
53	456536.1.dec	4591941H1	925	1184
53	456536.1.dec	g2055674	926	1224
53	456536.1.dec	g916274	926	1222
53	456536.1.dec	g4124213	927	1224
53	456536.1.dec	3981295H1	927	1202
53	456536.1.dec	3980095H1	928	1201
53	456536.1.dec	2512416H1	121	379
53	456536.1.dec	2725087H1	121	368
53	456536.1.dec	3112706H1	121	409
53	456536.1.dec	2822459H1	118	436
53	456536.1.dec	g2835002	866	1221
53	456536.1.dec	g2955714	867	1226
53	456536.1.dec	g2557444	964	1221
53	456536.1.dec	g2874235	964	1226
53	456536.1.dec	3691459H1	121	411
53	456536.1.dec	965168H1	121	402
53	456536.1.dec	1959390H1	121	374
53	456536.1.dec	3482520H1	118	456
53	456536.1.dec	g2670144	741	1221
53	456536.1.dec	2835861H1	741	1007
53	456536.1.dec	g2942564	744	1227
53	456536.1.dec	g3191676	750	1223

Table 4

53	456536.1.dec	g5425871	757	1220
53	456536.1.dec	5153284H1	758	865
53	456536.1.dec	4125006H1	758	945
53	456536.1.dec	1686462H1	758	972
53	456536.1.dec	758546R1	121	664
53	456536.1.dec	758546H1	121	389
53	456536.1.dec	2113769H1	121	386
53	456536.1.dec	1213489H1	702	942
53	456536.1.dec	g1386725	712	1095
53	456536.1.dec	g2064435	682	1100
53	456536.1.dec	2540285H1	689	926
53	456536.1.dec	g1977953	698	1076
53	456536.1.dec	g1383416	712	1028
53	456536.1.dec	1360265H1	716	954
53	456536.1.dec	637686H1	715	967
53	456536.1.dec	g2003985	737	1054
53	456536.1.dec	5993414H1	1	149
53	456536.1.dec	113167H1	46	210
53	456536.1.dec	2657989H1	45	278
53	456536.1.dec	g2563639	961	1241
53	456536.1.dec	g4268409	962	1230
53	456536.1.dec	g1774925	965	1152
53	456536.1.dec	g1690531	964	1193
53	456536.1.dec	3106368H1	953	1215
53	456536.1.dec	2091224H1	956	1190
53	456536.1.dec	g4876275	936	1222
53	456536.1.dec	g1470764	937	1222
53	456536.1.dec	4466881H1	939	1119
53	456536.1.dec	3146434H1	935	1206
53	456536.1.dec	g5365316	936	1221
53	456536.1.dec	g2069572	930	1226
53	456536.1.dec	3182477H1	934	1221
53	456536.1.dec	g2464429	854	1223
53	456536.1.dec	g4453913	855	949
53	456536.1.dec	g3042518	858	1224
53	456536.1.dec	g3076962	859	1221
53	456536.1.dec	g2555484	860	1214
53	456536.1.dec	g832016	862	1225
53	456536.1.dec	g3927282	865	1219
53	456536.1.dec	849449H1	95	356
53	456536.1.dec	g1470763	93	460
53	456536.1.dec	2616647H1	96	343
53	456536.1.dec	g3118059	893	1220
53	456536.1.dec	g3988602	893	1228
53	456536.1.dec	g3693926	894	1221
53	456536.1.dec	1292136H1	894	1152
53	456536.1.dec	g1383360	844	1220
53	456536.1.dec	g2254713	846	1221
53	456536.1.dec	6318065H1	848	1144
53	456536.1.dec	g3127629	850	1224
53	456536.1.dec	g517694	849	1221
53	456536.1.dec	814355T1	853	1182
53	456536.1.dec	814355H1	853	1084
53	456536.1.dec	814355R1	853	1221
53	456536.1.dec	992822H1	148	456
53	456536.1.dec	3470485H1	149	416
53	456536.1.dec	2874206H1	149	420
53	456536.1.dec	3180244H1	149	465
53	456536.1.dec	2478440H1	153	380
53	456536.1.dec	843190H1	163	395
53	456536.1.dec	3793502H1	163	458
53	456536.1.dec	2925558H1	163	445
53	456536.1.dec	2998580H1	153	402
53	456536.1.dec	3541085H1	153	433
53	456536.1.dec	g1146696	171	403
53	456536.1.dec	g2163374	171	580
53	456536.1.dec	4864007H1	648	930
53	456536.1.dec	g1303540	639	955
53	456536.1.dec	489544F1	652	1221
53	456536.1.dec	2503442H2	658	895
53	456536.1.dec	1959390T6	658	1175
53	456536.1.dec	6409986H1	666	1145
53	456536.1.dec	3344840H1	1127	1221
53	456536.1.dec	1001990H1	1159	1229
53	456536.1.dec	g1238126	1106	1224
53	456536.1.dec	5693765H1	1161	1219
53	456536.1.dec	860067H1	1093	1235
53	456536.1.dec	1858344H1	1105	1221
53	456536.1.dec	530775H1	121	368
53	456536.1.dec	2945472H1	121	220
53	456536.1.dec	2558137H1	121	226
53	456536.1.dec	638639H1	121	364
53	456536.1.dec	6299236H1	121	398
53	456536.1.dec	3458160H1	121	379
53	456536.1.dec	607838H1	147	422
53	456536.1.dec	607791H1	147	399
53	456536.1.dec	3369291H1	149	398
53	456536.1.dec	g2466663	883	1221
53	456536.1.dec	1969383H1	887	1097
53	456536.1.dec	g831904	892	1229
53	456536.1.dec	985686H1	121	212
53	456536.1.dec	2772065H1	124	372
53	456536.1.dec	1577745H1	124	343
53	456536.1.dec	2553453H1	121	371
53	456536.1.dec	2642987H1	121	314
53	456536.1.dec	g4606944	937	1221
53	456536.1.dec	1782414H1	904	1183
53	456536.1.dec	755891H1	904	1126
53	456536.1.dec	755891R1	904	1221
53	456536.1.dec	4369088H1	905	1176
53	456536.1.dec	g989963	908	1221
53	456536.1.dec	g2934621	964	1230
53	456536.1.dec	g1774926	964	1223
53	456536.1.dec	g2957365	964	1221
53	456536.1.dec	g3886653	965	1191
53	456536.1.dec	g3784917	971	1221
53	456536.1.dec	915765H1	976	1182
53	456536.1.dec	6377118H1	981	1213
53	456536.1.dec	g562504	986	1221
53	456536.1.dec	g691376	879	1214
53	456536.1.dec	2601535H1	92	375
53	456536.1.dec	3445778H2	91	352
53	456536.1.dec	1571555H1	92	305
53	456536.1.dec	2685889H1	92	277
53	456536.1.dec	2729095H1	91	324
53	456536.1.dec	1555001H1	92	311
53	456536.1.dec	527138H1	93	350
53	456536.1.dec	3416617H1	315	575
53	456536.1.dec	2270687H1	339	574
53	456536.1.dec	1685377H1	346	566
53	456536.1.dec	g2834102	364	566
53	456536.1.dec	3268340H1	365	594
53	456536.1.dec	1265564H1	394	683
53	456536.1.dec	g830474	122	428
53	456536.1.dec	446372H1	127	406
53	456536.1.dec	g1966035	125	411
53	456536.1.dec	2813111H1	128	444
53	456536.1.dec	g3038659	988	1221
53	456536.1.dec	g3145662	993	1222
53	456536.1.dec	g4901439	996	1210
53	456536.1.dec	g3148826	996	1209
53	456536.1.dec	2327682H1	998	1165
53	456536.1.dec	g762685	1006	1191
53	456536.1.dec	g671512	1010	1221

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53	456536.1.dec	g3039948	1092	1223
53	456536.1.dec	g791539	111	365
53	456536.1.dec	4408366H1	113	283
53	456536.1.dec	1559916H1	113	323
53	456536.1.dec	g671972	118	289
53	456536.1.dec	4115322H1	121	384
53	456536.1.dec	2408852H1	121	356
53	456536.1.dec	2551211H1	121	236
53	456536.1.dec	g2163212	795	1221
53	456536.1.dec	g1332029	801	1227
53	456536.1.dec	6096487H1	795	1077
53	456536.1.dec	g2986849	804	1225
53	456536.1.dec	g2341340	808	1221
53	456536.1.dec	g3804367	808	1214
53	456536.1.dec	g1382418	808	1230
53	456536.1.dec	346594H1	547	750
53	456536.1.dec	g2017833	558	929
53	456536.1.dec	g762177	92	307
53	456536.1.dec	1710041H1	93	343
53	456536.1.dec	3703053H1	93	397
53	456536.1.dec	526563H1	93	337
53	456536.1.dec	3357188H1	93	373
53	456536.1.dec	3493591H1	93	373
53	456536.1.dec	3402819H1	93	325
53	456536.1.dec	3181845H1	93	408
53	456536.1.dec	g1887396	235	355
53	456536.1.dec	3884276H1	267	530
53	456536.1.dec	2667252H1	268	522
53	456536.1.dec	3427814H1	111	335
53	456536.1.dec	3485715H1	108	407
53	456536.1.dec	2620446H1	112	366
53	456536.1.dec	g677182	90	294
53	456536.1.dec	3268726H1	91	338
53	456536.1.dec	g2837163	899	1221
53	456536.1.dec	g986639	902	1191
53	456536.1.dec	618412H1	904	1152
53	456536.1.dec	g1887333	1065	1221
53	456536.1.dec	g3004027	1072	1227
53	456536.1.dec	1982066H1	1082	1221
53	456536.1.dec	g1265864	1082	1221
53	456536.1.dec	g4265582	1088	1221
53	456536.1.dec	1830441H1	568	823
53	456536.1.dec	6291752H1	599	815
53	456536.1.dec	1620616H1	609	849
53	456536.1.dec	g4114551	612	999
53	456536.1.dec	5444332H1	633	877
53	456536.1.dec	4075596H1	633	905
53	456536.1.dec	3766586H1	94	383
53	456536.1.dec	2732225H1	95	355
53	456536.1.dec	2823702H1	96	402
53	456536.1.dec	913725H1	1012	1224
53	456536.1.dec	948147H1	1013	1215
53	456536.1.dec	g2325668	1023	1229
53	456536.1.dec	g3181113	1029	1223
53	456536.1.dec	g2102970	1043	1226
53	456536.1.dec	2987426H1	231	508
53	456536.1.dec	3377045H1	127	377
53	456536.1.dec	1899725H1	123	379
53	456536.1.dec	1900788H1	123	366
53	456536.1.dec	g1298038	126	378
53	456536.1.dec	449807H1	131	296
53	456536.1.dec	3460674H1	108	331
53	456536.1.dec	1751340H1	108	312
53	456536.1.dec	2110208H1	109	366
53	456536.1.dec	5865275H1	121	406
53	456536.1.dec	g831903	134	456
53	456536.1.dec	744457H1	135	388
53	456536.1.dec	2720282H1	143	389
53	456536.1.dec	992871H1	147	418
53	456536.1.dec	866692H1	148	413
53	456536.1.dec	2561964H1	133	402
53	456536.1.dec	2525342H1	134	384
53	456536.1.dec	3492927H1	134	405
53	456536.1.dec	3616606H1	134	403
53	456536.1.dec	2198749H1	135	285
53	456536.1.dec	1404036H1	97	354
53	456536.1.dec	489544R1	102	437
53	456536.1.dec	489544H1	102	361
53	456536.1.dec	2559140H1	101	357
53	456536.1.dec	1274175H1	104	239
53	456536.1.dec	1751413H1	108	323
53	456536.1.dec	1421202H1	107	290
53	456536.1.dec	g3899530	810	1219
53	456536.1.dec	g2952603	870	1227
53	456536.1.dec	3273308H1	74	322
53	456536.1.dec	g782097	74	255
53	456536.1.dec	2963221H1	91	392
53	456536.1.dec	3395218H1	89	364
53	456536.1.dec	2969539H1	91	363
53	456536.1.dec	3096426H1	94	389
53	456536.1.dec	3444439H1	97	367
53	456536.1.dec	3295828H1	99	360
53	456536.1.dec	1348565H1	100	230
53	456536.1.dec	3593237H1	99	388
53	456536.1.dec	3374783H1	97	358
53	456536.1.dec	g2055775	95	461
53	456536.1.dec	3620638H1	97	378
53	456536.1.dec	4714533H1	97	161
53	456536.1.dec	1299948H1	97	254
53	456536.1.dec	3160308H1	97	385
53	456536.1.dec	1754560H1	96	337
53	456536.1.dec	1319244H1	97	349
53	456536.1.dec	606322H1	97	385
53	456536.1.dec	g1988765	97	312
53	456536.1.dec	2833520H2	93	322
53	456536.1.dec	2565261H1	121	399
53	456536.1.dec	3358036H1	124	293
53	456536.1.dec	1784984H1	541	705
53	456536.1.dec	566397H1	545	824
53	456536.1.dec	3524691H1	547	847
53	456536.1.dec	2533048H1	481	818
53	456536.1.dec	5113612H1	490	786
53	456536.1.dec	1493584H1	493	713
53	456536.1.dec	6593451H1	504	995
53	456536.1.dec	1863502H1	496	782
53	456536.1.dec	1863502F6	496	1033
53	456536.1.dec	436142H1	504	603
53	456536.1.dec	3453989H1	534	806
53	456536.1.dec	2907327H1	540	739
53	456536.1.dec	5732233H1	415	685
53	456536.1.dec	4632451H1	426	684
53	456536.1.dec	g990010	428	684
53	456536.1.dec	2395270H1	438	665
53	456536.1.dec	1488271H1	479	743
53	456536.1.dec	4208981H1	404	537
53	456536.1.dec	4727980H1	417	678
53	456536.1.dec	2560321H1	401	663
53	456536.1.dec	1575881H1	70	187
53	456536.1.dec	3747523H1	70	371
53	456536.1.dec	1450986H1	69	322
53	456536.1.dec	3024440H1	69	312
53	456536.1.dec	2651171H1	73	208
53	456536.1.dec	1225060H1	57	292
53	456536.1.dec	6298584H1	64	309

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53	456536.1.dec	540325H1	67	275
53	456536.1.dec	3537964H1	68	368
53	456536.1.dec	3456808H1	68	311
53	456536.1.dec	3189412H1	70	389
53	456536.1.dec	g4899087	812	949
53	456536.1.dec	g3753281	812	1221
53	456536.1.dec	g3598298	812	1225
53	456536.1.dec	g4113780	812	1221
53	456536.1.dec	2202050H1	794	1047
53	456536.1.dec	1863502T6	794	1174
53	456536.1.dec	g3676957	787	1221
53	456536.1.dec	g2007458	779	1090
53	456536.1.dec	g2787281	782	949
53	456536.1.dec	g3649015	784	1227
53	456536.1.dec	1923568H1	761	1024
53	456536.1.dec	g3924137	763	1222
53	456536.1.dec	g2835063	763	1215
53	456536.1.dec	2752626H1	759	1037
53	456536.1.dec	g3330927	776	1217
53	456536.1.dec	1687386H1	833	1041
53	456536.1.dec	g4650333	834	949
53	456536.1.dec	6166167H1	843	1222
53	456536.1.dec	g5392951	841	1222
53	456536.1.dec	1982079T6	814	1180
53	456536.1.dec	1982079H1	814	1038
53	456536.1.dec	g2656831	813	1221
53	456536.1.dec	g2753183	815	949
53	456536.1.dec	1982079R6	814	1164
53	456536.1.dec	g4096028	831	949
53	456536.1.dec	g3924307	812	1214
54	387807.4.oct	3702147H1	1	291
54	387807.4.oct	g3307321	221	621
54	387807.4.oct	g3644993	223	518
54	387807.4.oct	g2836106	227	596
54	387807.4.oct	g3431952	226	573
54	387807.4.oct	g2714088	228	633
54	387807.4.oct	4560443T6	333	631
54	387807.4.oct	5980275H1	342	631
54	387807.4.oct	292878H1	416	521
54	387807.4.oct	1419003T6	427	527
54	387807.4.oct	5039911H1	498	740
54	387807.4.oct	4893519H1	536	615
54	387807.4.oct	4532934H1	638	889
54	387807.4.oct	3188491H1	643	867
54	387807.4.oct	3188491R6	643	986
54	387807.4.oct	2274775H1	643	798
54	387807.4.oct	1419003F6	643	1075
54	387807.4.oct	3491191H1	643	732
54	387807.4.oct	6322166H1	643	827
54	387807.4.oct	g1984547	654	954
54	387807.4.oct	5272773H1	683	764
54	387807.4.oct	5098260H1	697	962
54	387807.4.oct	4245582H1	784	1019
54	387807.4.oct	4403414H1	790	922
54	387807.4.oct	1419059H1	851	1075
54	387807.4.oct	1419003H1	861	1075
54	387807.4.oct	6102706H1	901	1194
54	387807.4.oct	g2629621	914	1312
54	387807.4.oct	2490348H1	1115	1342
54	387807.4.oct	3617390H1	1143	1339
55	406790.3.dec	366111H1	1	236
55	406790.3.dec	g2055030	2	422
55	406790.3.dec	2817564H1	16	272
55	406790.3.dec	3449061H1	17	259
55	406790.3.dec	995381R6	18	553
55	406790.3.dec	995381H1	18	326
55	406790.3.dec	6433084H1	45	462
55	406790.3.dec	5812480H1	19	295
55	406790.3.dec	3458385H1	19	249
55	406790.3.dec	6433130H1	45	638
55	406790.3.dec	995381T6	207	791
55	406790.3.dec	5594655H1	375	625
55	406790.3.dec	g2341498	402	767
55	406790.3.dec	g4664630	422	859
55	406790.3.dec	g5396183	431	859
55	406790.3.dec	g4311961	435	856
55	406790.3.dec	g3840805	503	859
56	412420.63.dec	g666234	1	279
56	412420.63.dec	g4487110	1	296
56	412420.63.dec	g1977452	1	228
56	412420.63.dec	g2805755	1	83
56	412420.63.dec	2898360H1	1	99
57	196623.3.dec	2517648H1	1	231
57	196623.3.dec	5686895H1	1	273
57	196623.3.dec	4645207H1	3	207
57	196623.3.dec	4605887H1	4	259
57	196623.3.dec	2901373F6	5	502
57	196623.3.dec	2901373H1	5	293
57	196623.3.dec	1394016F6	5	393
57	196623.3.dec	1600290H1	7	202
57	196623.3.dec	1394016H1	5	261
57	196623.3.dec	1395280H1	5	254
57	196623.3.dec	2696714H1	6	236
57	196623.3.dec	g2032778	11	208
57	196623.3.dec	3874480H1	13	267
57	196623.3.dec	5676590H1	15	276
57	196623.3.dec	5410878H1	17	272
57	196623.3.dec	1552649H1	17	210
57	196623.3.dec	4823454H1	18	179
57	196623.3.dec	4506764H1	26	295
57	196623.3.dec	4302206H1	24	279
57	196623.3.dec	6515768H1	30	490
57	196623.3.dec	2716365H1	26	286
57	196623.3.dec	5866818H1	27	279
57	196623.3.dec	3136703H1	26	312
57	196623.3.dec	3873631H1	26	330
57	196623.3.dec	3765014H1	28	321
57	196623.3.dec	3352194H1	26	281
57	196623.3.dec	2659790H1	26	252
57	196623.3.dec	4876834H1	29	300
57	196623.3.dec	3770415H1	29	341
57	196623.3.dec	4530091H1	31	274
57	196623.3.dec	1631018H1	29	147
57	196623.3.dec	5440130H1	32	245
57	196623.3.dec	3893567H1	31	199
57	196623.3.dec	3633822H1	33	314
57	196623.3.dec	2210577H1	32	291
57	196623.3.dec	4668793H1	34	297
57	196623.3.dec	3456796H1	33	274
57	196623.3.dec	223764R1	33	631
57	196623.3.dec	3833345H1	33	300
57	196623.3.dec	6377178H1	33	279
57	196623.3.dec	223764H1	33	256
57	196623.3.dec	225430H1	33	248
57	196623.3.dec	067067H1	33	178
57	196623.3.dec	g1728813	36	284
57	196623.3.dec	2403139H1	33	271
57	196623.3.dec	801372H1	38	259
57	196623.3.dec	2411122H1	38	254
57	196623.3.dec	3596160H1	38	312
57	196623.3.dec	067065H1	41	194
57	196623.3.dec	3584836H1	35	312
57	196623.3.dec	167565H1	56	371
57	196623.3.dec	3859670H1	58	338

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57	196623.3.dec	g2032705	59	366
57	196623.3.dec	g4737259	137	499
57	196623.3.dec	4092207H1	226	474
57	196623.3.dec	4581304H1	236	481
57	196623.3.dec	898109R6	241	647
57	196623.3.dec	898109H1	241	492
57	196623.3.dec	030943H1	568	844
57	196623.3.dec	2006252H1	568	727
57	196623.3.dec	3901332H1	581	810
57	196623.3.dec	2007562H1	655	838
57	196623.3.dec	3858113H1	759	1038
57	196623.3.dec	4422306H1	759	1021
58	427916.8.dec	1413110H1	1	161
58	427916.8.dec	1413110F6	1	457
58	427916.8.dec	2483841H1	1	196
58	427916.8.dec	1415706H1	1	182
58	427916.8.dec	g389421	1	251
58	427916.8.dec	4434759H1	26	282
58	427916.8.dec	5529558H1	32	309
58	427916.8.dec	3360746H1	34	291
58	427916.8.dec	3039830H1	87	370
58	427916.8.dec	5357136H1	138	317
58	427916.8.dec	5310884H1	161	386
58	427916.8.dec	2227664H1	163	341
58	427916.8.dec	4289094H1	212	340
59	264633.8.dec	2760074H1	2557	2829
59	264633.8.dec	5477979H1	2625	2764
59	264633.8.dec	g3041476	4970	5278
59	264633.8.dec	g2881327	5011	5285
59	264633.8.dec	4005052H2	3711	3945
59	264633.8.dec	g5123788	1	7677
59	264633.8.dec	2939613H1	1	92
59	264633.8.dec	g3839173	7222	7683
59	264633.8.dec	g3959822	7238	7663
59	264633.8.dec	g4332118	7244	7702
59	264633.8.dec	2203534H1	7461	7671
59	264633.8.dec	2753410R6	2446	3017
59	264633.8.dec	2753410H1	2446	2701
59	264633.8.dec	3669959H1	6210	6495
59	264633.8.dec	g2878174	4505	4894
59	264633.8.dec	6245402H1	4477	5044
59	264633.8.dec	027321H1	4504	4746
59	264633.8.dec	g2240505	4505	4917
59	264633.8.dec	4884709H1	4860	5051
59	264633.8.dec	g1736131	4841	5287
59	264633.8.dec	2053603H1	4841	5092
59	264633.8.dec	4825493H1	4851	5103
59	264633.8.dec	2047635H1	4815	5046
59	264633.8.dec	g2566999	4825	5246
59	264633.8.dec	2688383H1	4752	5008
59	264633.8.dec	g2705809	4781	5279
59	264633.8.dec	625590H1	4540	4777
59	264633.8.dec	3375634H1	4577	4814
59	264633.8.dec	2986212H1	4539	4795
59	264633.8.dec	1891014H1	4653	4935
59	264633.8.dec	3622936H1	4668	4948
59	264633.8.dec	5838668H1	7176	7397
59	264633.8.dec	2964536H1	7182	7478
59	264633.8.dec	5889738H1	6260	6544
59	264633.8.dec	5882902H1	6260	6547
59	264633.8.dec	2936459H1	7383	7655
59	264633.8.dec	g1010200	7376	7694
59	264633.8.dec	g1011545	7394	7674
59	264633.8.dec	g1026402	7401	7690
59	264633.8.dec	g2902950	4086	4337
59	264633.8.dec	2055804H1	4072	4329
59	264633.8.dec	g2788822	4078	4376
59	264633.8.dec	3580034F6	2957	3319
59	264633.8.dec	3580034H1	2959	3246
59	264633.8.dec	5273111H1	2974	3231
59	264633.8.dec	906926H1	3013	3173
59	264633.8.dec	1439286H1	3061	3307
59	264633.8.dec	169981R1	3092	3365
59	264633.8.dec	169981F1	3092	3366
59	264633.8.dec	169981H1	3092	3320
59	264633.8.dec	6493338H1	3130	3608
59	264633.8.dec	1320776H1	3138	3388
59	264633.8.dec	492151H1	3146	3409
59	264633.8.dec	3460677H1	3158	3381
59	264633.8.dec	4741080H1	3163	3370
59	264633.8.dec	5616847H1	3175	3284
59	264633.8.dec	6306822H1	3225	3669
59	264633.8.dec	5313464H1	3233	3301
59	264633.8.dec	1558226F6	3236	3491
59	264633.8.dec	3450312H1	3286	3532
59	264633.8.dec	1669451H1	3295	3526
59	264633.8.dec	6546636H1	3352	3785
59	264633.8.dec	2753410T6	3317	3910
59	264633.8.dec	5906384H1	3323	3596
59	264633.8.dec	g1736130	3367	3711
59	264633.8.dec	g1689800	3490	3578
59	264633.8.dec	3639891H1	3518	3788
59	264633.8.dec	4182954H1	3564	3754
59	264633.8.dec	5615577H1	3592	3879
59	264633.8.dec	4958507H1	3619	3783
59	264633.8.dec	g1558771	3639	4036
59	264633.8.dec	5084130H1	3643	3871
59	264633.8.dec	1645888F6	3673	4069
59	264633.8.dec	g5452540	4101	4355
59	264633.8.dec	g4987546	5067	5285
59	264633.8.dec	g1734159	5073	5285
59	264633.8.dec	1499149H1	5076	5285
59	264633.8.dec	6111175H1	5078	5329
59	264633.8.dec	2214010H1	5097	5342
59	264633.8.dec	2119572H1	5046	5289
59	264633.8.dec	3178947H1	5047	5285
59	264633.8.dec	g4738584	5049	5285
59	264633.8.dec	4888703H1	5064	5341
59	264633.8.dec	g2241797	7304	7680
59	264633.8.dec	g3843660	7321	7697
59	264633.8.dec	6386767H1	5770	6050
59	264633.8.dec	4547233H1	5699	5962
59	264633.8.dec	5193918F6	5913	6294
59	264633.8.dec	1903050H1	5043	5287
59	264633.8.dec	4706229H1	2406	2663
59	264633.8.dec	5193918H1	5913	6179
59	264633.8.dec	645727H1	5105	5362
59	264633.8.dec	861167H1	5222	5452
59	264633.8.dec	2834470H1	5222	5491
59	264633.8.dec	2263921H1	5231	5460
59	264633.8.dec	1669519H1	5280	5508
59	264633.8.dec	g3756312	4864	5285
59	264633.8.dec	g3734545	4143	4355
59	264633.8.dec	g2816934	4309	4376
59	264633.8.dec	g1558712	4905	5285
59	264633.8.dec	g4312948	4903	5217
59	264633.8.dec	g3896413	4922	5285
59	264633.8.dec	g3432963	4928	5285
59	264633.8.dec	g3753704	4930	5285
59	264633.8.dec	g3040420	3945	4355
59	264633.8.dec	g3917139	3960	4355
59	264633.8.dec	g3835247	3937	4355
59	264633.8.dec	g4896231	3944	4355
59	264633.8.dec	g1958739	7059	7443

Table 4

59	264633.8.dec	5153385H1	7130	7393
59	264633.8.dec	5735626H1	7042	7292
59	264633.8.dec	g2360618	7048	7445
59	264633.8.dec	5620491R8	4132	4404
59	264633.8.dec	g1713052	4134	4351
59	264633.8.dec	1645888H1	3673	3833
59	264633.8.dec	g3805397	3679	3967
59	264633.8.dec	009055R6	7360	7680
59	264633.8.dec	009055H1	7360	7608
59	264633.8.dec	g4453396	7361	7685
59	264633.8.dec	g1379240	7372	7680
59	264633.8.dec	6321696H1	1962	2237
59	264633.8.dec	3339964H1	2174	2441
59	264633.8.dec	4910157H1	1847	2112
59	264633.8.dec	g1977752	1628	1793
59	264633.8.dec	g5689516	1736	4405
59	264633.8.dec	g4076602	7402	7703
59	264633.8.dec	g5707037	7552	7689
59	264633.8.dec	2149426H1	7582	7674
59	264633.8.dec	1669010H1	5280	5510
59	264633.8.dec	g2008277	5382	5615
59	264633.8.dec	4178644H1	5659	5912
59	264633.8.dec	6181567H1	5672	5898
59	264633.8.dec	6209982H1	7225	7524
59	264633.8.dec	5020453T1	7252	7655
59	264633.8.dec	g3246288	7247	7684
59	264633.8.dec	g4982958	7248	7639
59	264633.8.dec	5193918T6	7257	7678
59	264633.8.dec	g2957486	7258	7445
59	264633.8.dec	055084H1	7269	7435
59	264633.8.dec	067973H1	7272	7458
59	264633.8.dec	3867461H1	6384	6511
59	264633.8.dec	5807225H1	6260	6491
59	264633.8.dec	g2589262	4437	4915
59	264633.8.dec	g4901330	4427	4874
59	264633.8.dec	g1928177	4469	4715
59	264633.8.dec	g1524709	4876	5295
59	264633.8.dec	1903050F6	4895	5287
59	264633.8.dec	5881559H1	6260	6525
59	264633.8.dec	5883369H1	6260	6522
59	264633.8.dec	2412358H1	6332	6579
59	264633.8.dec	5544024H1	6356	6554
59	264633.8.dec	4554593H1	6374	6601
59	264633.8.dec	260539H1	6383	6707
59	264633.8.dec	5566205H1	2764	3004
59	264633.8.dec	6357475H1	3978	4212
59	264633.8.dec	6327349H1	3978	4221
59	264633.8.dec	g775274	5955	6067
59	264633.8.dec	g3249712	273	7688
59	264633.8.dec	g319009	1369	1645
59	264633.8.dec	g1921891	1499	1947
59	264633.8.dec	g3595619	3924	4355
59	264633.8.dec	g4888293	3925	4392
59	264633.8.dec	009055T6	7360	7664
59	264633.8.dec	g4070420	4406	4896
59	264633.8.dec	g3803677	4406	4802
59	264633.8.dec	g4895931	4424	4889
59	264633.8.dec	g5595323	3970	4119
59	264633.8.dec	2872515H1	4676	4866
59	264633.8.dec	1740929H1	4711	4919
59	264633.8.dec	g1524770	4708	5139
59	264633.8.dec	2023182H1	4743	4996
59	264633.8.dec	g1734256	3862	3955
59	264633.8.dec	g2934347	3910	4337
59	264633.8.dec	g2433925	3739	3962
59	264633.8.dec	6544483H1	3772	4274
59	264633.8.dec	g4395405	3818	3955
59	264633.8.dec	4004375H1	3853	4015
59	264633.8.dec	3314920H1	3729	3960
59	264633.8.dec	g2567000	4974	5241
59	264633.8.dec	1903050T6	5000	5251
59	264633.8.dec	g5236647	3912	4366
59	264633.8.dec	g2908547	3915	4337
59	264633.8.dec	2831092H1	3928	4003
59	264633.8.dec	5882023H1	6260	6521
59	264633.8.dec	5887277H1	6260	6462
59	264633.8.dec	3931164H1	6224	6500
59	264633.8.dec	5545540H1	2633	2828
59	264633.8.dec	5546368H1	2643	2831
59	264633.8.dec	g4522792	7268	7680
59	264633.8.dec	3839760H1	7275	7566
59	264633.8.dec	g1623287	7296	7693
59	264633.8.dec	g752466	7403	7674
59	264633.8.dec	g991482	7401	7663
59	264633.8.dec	g2877698	3985	4337
59	264633.8.dec	g2876827	4035	4228
59	264633.8.dec	2055804R6	4072	4354
59	264633.8.dec	g5529021	3985	4355
59	264633.8.dec	401718H1	7001	7266
59	264633.8.dec	g5591949	7006	7283
59	264633.8.dec	g2328920	7012	7445
59	264633.8.dec	2649891H1	7029	7282
59	264633.8.dec	g1623286	6986	7305
59	264633.8.dec	g2902964	6987	7454
59	264633.8.dec	5020453H1	6854	6978
59	264633.8.dec	5093687H1	6891	7158
59	264633.8.dec	g1026722	6895	7268
59	264633.8.dec	g1025017	6895	7114
59	264633.8.dec	5094369H1	6929	7172
59	264633.8.dec	2653154H1	6938	7179
59	264633.8.dec	3172174H1	6957	7172
59	264633.8.dec	6209435H1	6983	7251
59	264633.8.dec	2518677H1	6984	7221
59	264633.8.dec	2896833H1	6696	6972
59	264633.8.dec	g752465	6709	6988
59	264633.8.dec	3403481H1	6715	6956
59	264633.8.dec	5040507H1	6715	6952
59	264633.8.dec	5041590H1	6716	6961
59	264633.8.dec	3988731H1	6719	7004
59	264633.8.dec	3645638H1	6726	7013
59	264633.8.dec	1891273H1	6729	6974
59	264633.8.dec	946530H1	6745	6979
59	264633.8.dec	g1011156	6786	7036
59	264633.8.dec	6593361H1	6814	7223
59	264633.8.dec	g4243143	6816	7273
59	264633.8.dec	4212002H1	6845	7124
59	264633.8.dec	1489550F6	6537	7023
59	264633.8.dec	1489550H1	6537	6790
59	264633.8.dec	4501054H1	6558	6794
59	264633.8.dec	3044125H1	6579	6853
59	264633.8.dec	5452322H1	6584	6835
59	264633.8.dec	g1010248	6586	6884
59	264633.8.dec	g1010260	6587	6825
59	264633.8.dec	1470385F6	6641	7087
59	264633.8.dec	1470385H1	6641	6830
59	264633.8.dec	3606436H1	6642	6866
59	264633.8.dec	5025468H1	6675	6967
59	264633.8.dec	5150604H1	6679	6934
59	264633.8.dec	1456829H1	6687	6916
59	264633.8.dec	5913938H1	6529	6783
59	264633.8.dec	g2254985	7461	7682
59	264633.8.dec	g4378013	33	7691
59	264633.8.dec	g1976686	74	399
59	264633.8.dec	3358612H1	6392	6669

Table 4

59	264633.8.dec	g990828	6479	6830
59	264633.8.dec	4522981H1	4965	5221
59	264633.8.dec	g2255600	7326	7680
59	264633.8.dec	g5446131	7336	7683
59	264633.8.dec	g4222673	7348	7681
59	264633.8.dec	g3043107	3694	3955
59	264633.8.dec	5731062H1	6047	6250
59	264633.8.dec	3584229H1	6063	6331
59	264633.8.dec	g2014008	6133	6423
59	264633.8.dec	626375H1	6029	6230
59	264633.8.dec	626519H1	6029	6136
59	264633.8.dec	1489550T6	7421	7653
59	264633.8.dec	5478430H1	5957	6209
59	264633.8.dec	g900129	5978	6314
59	264633.8.dec	g908380	6015	6283
59	264633.8.dec	5889703H1	6260	6456
59	264633.8.dec	5882091H1	6260	6342
59	264633.8.dec	5884167H1	6261	6515
59	264633.8.dec	g3797785	4931	5290
59	264633.8.dec	g1689718	4957	5286
59	264633.8.dec	g3015912	4959	5290
59	264633.8.dec	6008118H1	7417	7680
59	264633.8.dec	2556025H1	7412	7642
60	337822.4.dec	g3755755	581	888
60	337822.4.dec	g667395	768	882
60	337822.4.dec	2833833H1	823	1081
60	337822.4.dec	g395543	941	1212
60	337822.4.dec	g2825241	1067	1260
60	337822.4.dec	g2064264	1102	1430
60	337822.4.dec	2915382H1	7	140
60	337822.4.dec	g1269991	26	194
60	337822.4.dec	g875782	172	415
60	337822.4.dec	g3283993	210	1576
60	337822.4.dec	g5110760	423	884
60	337822.4.dec	g3753613	474	883
60	337822.4.dec	4740515H2	558	827
60	337822.4.dec	4738945H1	558	705
60	337822.4.dec	2080490H1	1140	1413
60	337822.4.dec	3280776H1	1	181
60	337822.4.dec	2915382F6	1	318
60	337822.4.dec	3252911H1	5	250
61	902943.1.dec	5638959H1	1	209
61	902943.1.dec	6491718H1	157	634
61	902943.1.dec	2415341T6	518	1042
61	902943.1.dec	6428735H1	867	1184
61	902943.1.dec	g2834117	922	1236
61	902943.1.dec	6426168H1	943	1312
61	902943.1.dec	5639272H1	1027	1265
61	902943.1.dec	5642514R8	1089	1441
61	902943.1.dec	6492034H1	1167	1686
61	902943.1.dec	358895H1	1444	1689
61	902943.1.dec	6487975H1	1578	2076
61	902943.1.dec	5091951H1	1586	1649
61	902943.1.dec	6264350H1	1694	1873
61	902943.1.dec	4455276F6	1739	2225
61	902943.1.dec	4455276H1	1739	1979
61	902943.1.dec	5089810H1	1977	2265
61	902943.1.dec	6344967H1	2005	2274
61	902943.1.dec	6171524H1	2010	2321
61	902943.1.dec	6005774H1	2069	2358
61	902943.1.dec	3426344F6	2093	2452
61	902943.1.dec	3426344H1	2095	2334
61	902943.1.dec	5642539H1	2204	2370
61	902943.1.dec	6427209H1	2208	2810
61	902943.1.dec	5627532H1	2226	2466
61	902943.1.dec	g2243717	2295	2559
61	902943.1.dec	4284624H1	2302	2557
61	902943.1.dec	6490801H1	2516	3033
61	902943.1.dec	6489463H1	2547	3084
61	902943.1.dec	g2012148	2641	2972
61	902943.1.dec	6486889H1	2688	3182
61	902943.1.dec	6482904H1	2760	3106
61	902943.1.dec	5873213H1	2866	3167
61	902943.1.dec	5873221H1	2870	3167
61	902943.1.dec	6432615H1	3109	3555
61	902943.1.dec	6354243H1	3330	3608
61	902943.1.dec	5637909H1	3334	3554
61	902943.1.dec	5644969H1	3344	3574
61	902943.1.dec	4457090H1	3364	3563
61	902943.1.dec	5642514H1	3386	3612
61	902943.1.dec	6170624H1	3511	3821
61	902943.1.dec	5092668F6	3637	4104
61	902943.1.dec	5092668H1	3637	3784
61	902943.1.dec	4455573H1	3665	3908
61	902943.1.dec	2415341H1	3936	4126
61	902943.1.dec	2415341F6	3936	4297
61	902943.1.dec	5644569R8	4000	4363
61	902943.1.dec	5637811H1	3999	4232
61	902943.1.dec	5092668R6	4232	4744
61	902943.1.dec	4455573R8	4303	4499
62	256009.2.dec	3686313H1	6803	7062
62	256009.2.dec	2895979H1	6802	7098
62	256009.2.dec	2129702H1	6804	7076
62	256009.2.dec	1655677H1	6803	7029
62	256009.2.dec	g2021489	6804	7082
62	256009.2.dec	2884943H1	6804	7059
62	256009.2.dec	3637254H1	6804	7017
62	256009.2.dec	854050H1	6804	7046
62	256009.2.dec	3243241H1	6803	7045
62	256009.2.dec	3693242H1	6804	7085
62	256009.2.dec	609587H1	6804	7050
62	256009.2.dec	g4664567	6805	7221
62	256009.2.dec	2172480H1	6807	7062
62	256009.2.dec	2228032H1	6804	7033
62	256009.2.dec	5915452H1	6804	7079
62	256009.2.dec	1373349H1	6804	7037
62	256009.2.dec	3433122H1	6803	7045
62	256009.2.dec	5293637H2	6808	7047
62	256009.2.dec	2272963H1	6806	7072
62	256009.2.dec	1687974H1	6806	7053
62	256009.2.dec	2317928H1	6806	7019
62	256009.2.dec	854024H1	6804	6999
62	256009.2.dec	1616977H1	6805	7024
62	256009.2.dec	726262H1	6805	7031
62	256009.2.dec	3254175H1	6805	7027
62	256009.2.dec	4950837H1	6806	7083
62	256009.2.dec	3098257H1	6805	7101
62	256009.2.dec	3015006H1	6806	7089
62	256009.2.dec	1544438R6	6806	7187
62	256009.2.dec	1227986H1	6806	7043
62	256009.2.dec	2729617H1	6806	7063
62	256009.2.dec	1385926H1	6807	7020
62	256009.2.dec	2079647H1	6806	7056
62	256009.2.dec	6543764H1	6809	7200
62	256009.2.dec	g1954438	6809	7194
62	256009.2.dec	1293789H1	6808	7027
62	256009.2.dec	1417792H1	6808	7022
62	256009.2.dec	2741429H1	6808	7060
62	256009.2.dec	3391859H1	6806	7099
62	256009.2.dec	4083084H1	6806	7065
62	256009.2.dec	758913H1	6809	7082
62	256009.2.dec	2730231H1	6806	7041
62	256009.2.dec	605554H1	6808	7050
62	256009.2.dec	924108H1	6809	7019

Table 4

62	256009.2.dec	599887H1	6806	7048
62	256009.2.dec	1293789F1	6808	7215
62	256009.2.dec	2266615H1	6808	7046
62	256009.2.dec	1581702H1	6809	7005
62	256009.2.dec	2242319H1	6808	7057
62	256009.2.dec	4046218H1	6809	7104
62	256009.2.dec	1875482H1	6809	7054
62	256009.2.dec	2454454H1	6809	7043
62	256009.2.dec	4227366H1	6806	6910
62	256009.2.dec	865153H1	6806	7065
62	256009.2.dec	3705575H1	6808	7091
62	256009.2.dec	2921451H1	6808	7092
62	256009.2.dec	3012201H1	6809	7097
62	256009.2.dec	2238257H1	6807	7068
62	256009.2.dec	5174485H1	6809	7070
62	256009.2.dec	3291912H1	6809	7075
62	256009.2.dec	4739453H1	6809	7022
62	256009.2.dec	4506287H1	6808	7075
62	256009.2.dec	1544435H1	6808	7001
62	256009.2.dec	805905H1	6809	7024
62	256009.2.dec	4210490H1	6808	7073
62	256009.2.dec	3430794H1	6808	7047
62	256009.2.dec	712348H1	6809	6992
62	256009.2.dec	4454989H1	6808	7051
62	256009.2.dec	646904H1	6809	7022
62	256009.2.dec	1581619H1	6809	6985
62	256009.2.dec	5287054H1	6808	7061
62	256009.2.dec	1543140H1	6809	7002
62	256009.2.dec	2771665H1	6809	7055
62	256009.2.dec	2223625H1	6809	6983
62	256009.2.dec	5887790H1	6809	7069
62	256009.2.dec	918247H1	6809	7021
62	256009.2.dec	2486090H1	6809	7030
62	256009.2.dec	1225955H1	6809	7029
62	256009.2.dec	1255796H1	6809	7037
62	256009.2.dec	1500991H1	6809	6995
62	256009.2.dec	1591365H1	6809	7038
62	256009.2.dec	918252R1	6809	7206
62	256009.2.dec	645991H1	6809	7019
62	256009.2.dec	1255141H1	6809	7046
62	256009.2.dec	691144H1	6809	7068
62	256009.2.dec	2626844H1	6809	7044
62	256009.2.dec	1957222H1	6809	7045
62	256009.2.dec	4080495H1	6810	7073
62	256009.2.dec	5598895H1	6809	7009
62	256009.2.dec	957630T1	6809	7178
62	256009.2.dec	2029004H1	6809	7069
62	256009.2.dec	3370122H1	6809	7084
62	256009.2.dec	907620T1	6809	7179
62	256009.2.dec	3169225H1	6809	7091
62	256009.2.dec	4018584H1	6809	7093
62	256009.2.dec	5886851H1	6809	7063
62	256009.2.dec	2726816H1	6809	7058
62	256009.2.dec	5168407H1	6809	7060
62	256009.2.dec	2081887H1	6809	7063
62	256009.2.dec	2627004H1	6809	7052
62	256009.2.dec	1864684H1	6809	7064
62	256009.2.dec	907620R2	6809	7215
62	256009.2.dec	2218517H1	6809	7050
62	256009.2.dec	1992968H1	6809	7001
62	256009.2.dec	1865389H1	6809	7068
62	256009.2.dec	2053436H1	6809	7059
62	256009.2.dec	3809520H1	6809	7103
62	256009.2.dec	907620H1	6809	7103
62	256009.2.dec	1867532H1	6809	6992
62	256009.2.dec	3015059H1	6809	7107
62	256009.2.dec	2148431H1	6809	7048
62	256009.2.dec	2079972H1	6809	7072
62	256009.2.dec	3168974H1	6809	7005
62	256009.2.dec	6541086H1	6809	7215
62	256009.2.dec	1915024H1	6809	7052
62	256009.2.dec	3010414H1	6809	7101
62	256009.2.dec	3366620H1	6809	7080
62	256009.2.dec	2920709H2	6809	7084
62	256009.2.dec	3982991H1	6809	7078
62	256009.2.dec	2307565H1	6809	7027
62	256009.2.dec	3685780H1	6809	7027
62	256009.2.dec	990361H1	6809	7081
62	256009.2.dec	1704728H1	6809	6980
62	256009.2.dec	1968166H1	6809	7087
62	256009.2.dec	5794878H1	6809	7044
62	256009.2.dec	1318627H1	6809	7032
62	256009.2.dec	1543140T1	6809	7170
62	256009.2.dec	1209524R1	6809	7215
62	256009.2.dec	3042117H1	6809	7047
62	256009.2.dec	2364635H1	6809	7029
62	256009.2.dec	3013148H1	6809	7031
62	256009.2.dec	3199578H1	6809	6917
62	256009.2.dec	4058217H1	6814	7091
62	256009.2.dec	726606H1	6814	7028
62	256009.2.dec	1844481H1	6814	7063
62	256009.2.dec	3942420H1	6814	6991
62	256009.2.dec	853931H1	6814	6978
62	256009.2.dec	2413378H1	6813	7026
62	256009.2.dec	2766178H1	6814	6946
62	256009.2.dec	808678H1	6814	7089
62	256009.2.dec	2778183H1	6814	7044
62	256009.2.dec	2545037H2	6814	7084
62	256009.2.dec	796402R1	6814	7208
62	256009.2.dec	1284285H1	6814	7070
62	256009.2.dec	808678R1	6814	7215
62	256009.2.dec	3040759H1	6814	7106
62	256009.2.dec	6377702H1	6814	7106
62	256009.2.dec	990071H1	6816	7155
62	256009.2.dec	1259740H1	6814	6945
62	256009.2.dec	2923289H1	6814	7054
62	256009.2.dec	4165467H1	6815	7100
62	256009.2.dec	591114H1	6814	6992
62	256009.2.dec	2586985H1	6814	7069
62	256009.2.dec	g1365385	6816	7226
62	256009.2.dec	3170840H1	6815	7098
62	256009.2.dec	1657713H1	6814	6994
62	256009.2.dec	584601H1	6816	7060
62	256009.2.dec	714218H1	6814	7041
62	256009.2.dec	1496788H1	6816	7024
62	256009.2.dec	1722939H1	6816	7069
62	256009.2.dec	4405027H1	6815	7085
62	256009.2.dec	856073R6	6816	6947
62	256009.2.dec	1283845H1	6816	7090
62	256009.2.dec	2800890H1	6816	7078
62	256009.2.dec	990071R1	6816	7195
62	256009.2.dec	2837884H1	6816	7058
62	256009.2.dec	820298H1	6816	7109
62	256009.2.dec	3960201H2	6816	7087
62	256009.2.dec	1001763H1	6816	7093
62	256009.2.dec	990071T1	6816	7177
62	256009.2.dec	688055H1	6816	7090
62	256009.2.dec	1967463H1	6816	7098
62	256009.2.dec	1993519H1	6816	7000
62	256009.2.dec	1359721H1	6814	6991
62	256009.2.dec	1001763R1	6816	7214
62	256009.2.dec	2690995H1	6816	7052
62	256009.2.dec	5171812F6	6817	7215
62	256009.2.dec	3779566H1	6816	7108

Table 4

62	256009.2.dec	1910133H1	6819	7050
62	256009.2.dec	2884456H1	6819	7091
62	256009.2.dec	g5366891	6819	7223
62	256009.2.dec	g3805623	6819	7221
62	256009.2.dec	4306424H1	6819	7107
62	256009.2.dec	g5363952	6819	7220
62	256009.2.dec	6587039H1	6819	7156
62	256009.2.dec	711967H1	6820	7036
62	256009.2.dec	g2834392	6819	7215
62	256009.2.dec	2328184H1	6820	7060
62	256009.2.dec	2561102H1	6820	7093
62	256009.2.dec	195463H1	6821	6988
62	256009.2.dec	2996434H1	6820	7050
62	256009.2.dec	4185190H1	6820	7156
62	256009.2.dec	2780680H2	6820	7008
62	256009.2.dec	2259974H1	6820	7068
62	256009.2.dec	g1924526	6820	7128
62	256009.2.dec	1476613H1	6821	7070
62	256009.2.dec	1726084T6	6821	7184
62	256009.2.dec	1337992H1	6821	7020
62	256009.2.dec	1682252T7	6821	7167
62	256009.2.dec	1359209H1	6822	7067
62	256009.2.dec	060152H1	6822	6994
62	256009.2.dec	232161H1	6822	7155
62	256009.2.dec	6407668H1	6822	7074
62	256009.2.dec	6407636H1	6822	7061
62	256009.2.dec	3408813H1	6825	7063
62	256009.2.dec	2487681H1	6827	7053
62	256009.2.dec	g4889718	6826	7220
62	256009.2.dec	g1987626	6827	7204
62	256009.2.dec	g1987624	6827	7180
62	256009.2.dec	1425242H1	6827	7077
62	256009.2.dec	3098659H1	6826	7125
62	256009.2.dec	009294H1	6827	7112
62	256009.2.dec	g2194854	6827	7203
62	256009.2.dec	638747H1	6827	7091
62	256009.2.dec	705477H1	6828	7079
62	256009.2.dec	1568307H1	6828	7031
62	256009.2.dec	1781381H1	6828	7066
62	256009.2.dec	1571440H1	6828	7028
62	256009.2.dec	g4565404	6830	7221
62	256009.2.dec	g4703912	6832	7216
62	256009.2.dec	617791H1	6832	7065
62	256009.2.dec	6592449H1	6832	7218
62	256009.2.dec	5164934H1	6833	7095
62	256009.2.dec	5071984H1	6834	7121
62	256009.2.dec	382723H1	6837	7058
62	256009.2.dec	4180764H1	6837	7105
62	256009.2.dec	849037H1	6837	7054
62	256009.2.dec	g3957743	6836	7119
62	256009.2.dec	g3741345	6836	7215
62	256009.2.dec	g2005160	6837	7199
62	256009.2.dec	782337R1	6836	7220
62	256009.2.dec	3995839H1	6834	7130
62	256009.2.dec	782337H1	6836	7065
62	256009.2.dec	4729332H1	6836	6923
62	256009.2.dec	849037T1	6837	7179
62	256009.2.dec	4624859H1	6837	7054
62	256009.2.dec	3752695H1	6836	7097
62	256009.2.dec	2553947H1	6837	7085
62	256009.2.dec	g1384814	6837	7216
62	256009.2.dec	g3745176	6838	7220
62	256009.2.dec	2316580H1	6840	7083
62	256009.2.dec	g3047695	6840	7218
62	256009.2.dec	1678739H1	6840	7060
62	256009.2.dec	009111H1	6841	7197
62	256009.2.dec	2023418H1	6841	7052
62	256009.2.dec	g2269938	6841	7216
62	256009.2.dec	463130H1	6842	7061
62	256009.2.dec	3803431H1	6816	7033
62	256009.2.dec	913629H1	6817	7050
62	256009.2.dec	972591H1	6817	7112
62	256009.2.dec	g1638139	6816	6964
62	256009.2.dec	g5366184	6843	7212
62	256009.2.dec	3449063H1	6817	7018
62	256009.2.dec	1907880H1	6819	7089
62	256009.2.dec	g1390452	6844	7077
62	256009.2.dec	g2839645	6843	7219
62	256009.2.dec	g2539812	6843	7218
62	256009.2.dec	g1442388	6845	7059
62	256009.2.dec	g1492911	6844	7012
62	256009.2.dec	g2584157	6845	7215
62	256009.2.dec	1711465H1	6845	7066
62	256009.2.dec	896723H1	6845	7036
62	256009.2.dec	711668H1	6845	7071
62	256009.2.dec	4215980H1	6845	7084
62	256009.2.dec	4542159H1	6845	7061
62	256009.2.dec	1879840H1	6845	7088
62	256009.2.dec	g1634214	6847	7228
62	256009.2.dec	5020933T1	6847	7176
62	256009.2.dec	918292R1	6849	7215
62	256009.2.dec	1858904H1	6809	7048
62	256009.2.dec	1426132H1	6809	7063
62	256009.2.dec	1572120H1	6809	6997
62	256009.2.dec	2841084H1	6809	7078
62	256009.2.dec	6545425H1	6809	7215
62	256009.2.dec	421303H1	6809	7086
62	256009.2.dec	5098032H1	6809	7040
62	256009.2.dec	4126959H1	6809	7047
62	256009.2.dec	2589220H1	6809	7033
62	256009.2.dec	6193555H1	6809	7079
62	256009.2.dec	3348521H1	6809	7074
62	256009.2.dec	1209525H1	6809	7035
62	256009.2.dec	3624280H1	6809	7036
62	256009.2.dec	1798023H1	6809	6944
62	256009.2.dec	2448821H1	6809	7036
62	256009.2.dec	971894H1	6809	7105
62	256009.2.dec	4653692H1	6809	7076
62	256009.2.dec	4084177H1	6809	7082
62	256009.2.dec	5790781H1	6809	7103
62	256009.2.dec	805905T1	6809	7177
62	256009.2.dec	2738926H1	6809	7039
62	256009.2.dec	3552248H1	6809	7048
62	256009.2.dec	1754254H1	6809	7039
62	256009.2.dec	1335049H1	6809	7073
62	256009.2.dec	1569773H1	6808	7008
62	256009.2.dec	1818743H1	6809	7073
62	256009.2.dec	g1687094	6809	7202
62	256009.2.dec	5194662T6	6809	7204
62	256009.2.dec	3122117H1	6809	7117
62	256009.2.dec	710232H1	6809	7063
62	256009.2.dec	1528530H1	6809	7008
62	256009.2.dec	2685153H1	6809	7066
62	256009.2.dec	1988864H1	6809	7009
62	256009.2.dec	5790126H1	6809	7101
62	256009.2.dec	1815060H1	6809	7072
62	256009.2.dec	3013278H1	6809	7099
62	256009.2.dec	2751927H1	6809	7070
62	256009.2.dec	902835H1	6809	7107
62	256009.2.dec	3048722H1	6809	7116
62	256009.2.dec	806953H1	6809	7061
62	256009.2.dec	957630H1	6809	7054
62	256009.2.dec	935771H1	6809	7065
62	256009.2.dec	1887355H1	6809	7071

Table 4

62	256009.2.dec	5785036H1	6809	7095
62	256009.2.dec	2748363H1	6809	7071
62	256009.2.dec	629827H1	6809	7059
62	256009.2.dec	2632019H1	6809	7055
62	256009.2.dec	3091228H1	6809	7091
62	256009.2.dec	4300892H1	6809	7066
62	256009.2.dec	5489154H1	6808	6990
62	256009.2.dec	1899411H1	6809	7062
62	256009.2.dec	5060193H1	6809	7090
62	256009.2.dec	972090H1	6809	7001
62	256009.2.dec	586858H1	6809	7063
62	256009.2.dec	2297454H1	6809	6903
62	256009.2.dec	1253701H1	6809	6948
62	256009.2.dec	1315631H1	6809	6949
62	256009.2.dec	5345844H1	6809	7042
62	256009.2.dec	3037654H1	6811	6991
62	256009.2.dec	3943490H1	6810	7074
62	256009.2.dec	1316820H1	6809	7037
62	256009.2.dec	1316792H1	6809	7053
62	256009.2.dec	3406855H1	6810	7071
62	256009.2.dec	819837H1	6810	7047
62	256009.2.dec	862304H1	6809	7061
62	256009.2.dec	2276745H1	6809	7082
62	256009.2.dec	990385H1	6809	7130
62	256009.2.dec	2121103H1	6811	7064
62	256009.2.dec	3049389H1	6809	7042
62	256009.2.dec	3601234H1	6810	7105
62	256009.2.dec	908681H1	6809	7101
62	256009.2.dec	3880787H1	6810	7086
62	256009.2.dec	3011719H1	6810	7088
62	256009.2.dec	2600096H1	6810	7088
62	256009.2.dec	2924309H1	6809	7080
62	256009.2.dec	5791558H1	6809	7085
62	256009.2.dec	3283883H1	6810	7051
62	256009.2.dec	4153912H1	6809	7076
62	256009.2.dec	3047406H1	6810	7104
62	256009.2.dec	5885375H1	6810	7062
62	256009.2.dec	4239810H1	6810	6989
62	256009.2.dec	589315H1	6809	7048
62	256009.2.dec	4185609H1	6809	7107
62	256009.2.dec	2812373H1	6809	7072
62	256009.2.dec	2520870H1	6811	7052
62	256009.2.dec	3884579H1	6810	7043
62	256009.2.dec	1845847H1	6809	6995
62	256009.2.dec	2708924H1	6809	7122
62	256009.2.dec	4046820H1	6809	7089
62	256009.2.dec	1960912H1	6809	7085
62	256009.2.dec	3049275H1	6810	7097
62	256009.2.dec	3215251H1	6810	7100
62	256009.2.dec	4365729H1	6811	7073
62	256009.2.dec	4117120H1	6814	6975
62	256009.2.dec	g2194573	6811	7181
62	256009.2.dec	5091046H1	6811	7076
62	256009.2.dec	1857590H1	6811	7073
62	256009.2.dec	1695556H1	6811	7024
62	256009.2.dec	869832H1	6811	7070
62	256009.2.dec	2318919H1	6811	7078
62	256009.2.dec	1693022H1	6811	7017
62	256009.2.dec	1273812F1	6812	7215
62	256009.2.dec	2367176H1	6810	7031
62	256009.2.dec	824777H1	6811	7127
62	256009.2.dec	3114091H1	6810	7084
62	256009.2.dec	824777T1	6811	7173
62	256009.2.dec	g2265297	6811	7217
62	256009.2.dec	704635H1	6811	7037
62	256009.2.dec	5090855H1	6811	7086
62	256009.2.dec	1496555H1	6811	7034
62	256009.2.dec	1317325H1	6811	7069
62	256009.2.dec	571696H1	6812	7045
62	256009.2.dec	824777R1	6812	7215
62	256009.2.dec	1997827H1	6814	7084
62	256009.2.dec	1273812H1	6812	7054
62	256009.2.dec	869832R1	6812	7215
62	256009.2.dec	1273829H1	6812	7049
62	256009.2.dec	3171537H1	6811	7081
62	256009.2.dec	5879195H1	6812	7083
62	256009.2.dec	799290H1	6812	7053
62	256009.2.dec	801133H1	6813	7053
62	256009.2.dec	2257124H1	6812	7028
62	256009.2.dec	1968416H1	6812	7084
62	256009.2.dec	g1497186	6813	7025
62	256009.2.dec	586836H1	6814	7028
62	256009.2.dec	1752747H1	6813	7075
62	256009.2.dec	991986H1	6813	7101
62	256009.2.dec	1416160H1	6813	7052
62	256009.2.dec	2079716H1	6813	6972
62	256009.2.dec	g4890156	6813	7219
62	256009.2.dec	5297941H1	6814	6930
62	256009.2.dec	3220925H1	6813	7119
62	256009.2.dec	g1270234	6813	7137
62	256009.2.dec	2346929H1	6813	7016
62	256009.2.dec	5391711H1	6813	7101
62	256009.2.dec	2230794H1	6813	7026
62	256009.2.dec	218469H1	6814	7049
62	256009.2.dec	4373191H1	6523	6774
62	256009.2.dec	871243H1	6525	6764
62	256009.2.dec	2972356H1	6534	6661
62	256009.2.dec	463304H1	6541	6702
62	256009.2.dec	4625565F6	6555	6902
62	256009.2.dec	5114016H1	6556	6845
62	256009.2.dec	3947921H1	6572	6743
62	256009.2.dec	1682252F7	6575	6865
62	256009.2.dec	1682252H1	6575	6750
62	256009.2.dec	1682229H1	6575	6757
62	256009.2.dec	2932355H1	6581	6811
62	256009.2.dec	6408071H1	6586	6769
62	256009.2.dec	1499581H1	6585	6793
62	256009.2.dec	4362986H1	6590	6842
62	256009.2.dec	5044811H1	6592	6730
62	256009.2.dec	3706863H1	6592	6885
62	256009.2.dec	2659266H1	6599	6829
62	256009.2.dec	4359709H1	6599	6852
62	256009.2.dec	5375710H1	6602	6861
62	256009.2.dec	4109048H1	6620	6900
62	256009.2.dec	3740282T6	6621	7168
62	256009.2.dec	1227552H1	6624	6832
62	256009.2.dec	1263359H1	6641	6909
62	256009.2.dec	1263359R1	6642	7181
62	256009.2.dec	1601346T6	6643	7179
62	256009.2.dec	5286950H1	6645	6822
62	256009.2.dec	6587440H1	6645	7200
62	256009.2.dec	3988491H1	6650	6925
62	256009.2.dec	6396383H1	6650	6960
62	256009.2.dec	2121123H1	6651	6897
62	256009.2.dec	3963377H1	6651	6936
62	256009.2.dec	3965396H1	6651	6842
62	256009.2.dec	5281655H1	6658	6873
62	256009.2.dec	3170987H1	6666	6925
62	256009.2.dec	1260390H1	6666	6901
62	256009.2.dec	5577548H1	6668	6923
62	256009.2.dec	818983R1	6671	7223
62	256009.2.dec	818983T1	6671	7176
62	256009.2.dec	818983H1	6671	6859
62	256009.2.dec	2049005H1	6672	6955

Table 4

62	256009.2.dec	870733H1	6672	6917	62	256009.2.dec	1301095H1	6800	7056
62	256009.2.dec	990641H1	6674	6982	62	256009.2.dec	3389837H1	6800	7061
62	256009.2.dec	947048H1	6677	6832	62	256009.2.dec	4229811H1	6800	7084
62	256009.2.dec	206785H1	6677	6908	62	256009.2.dec	g1365272	6801	7224
62	256009.2.dec	g1506961	6694	6872	62	256009.2.dec	933491T1	6800	7177
62	256009.2.dec	5006831H1	6694	6807	62	256009.2.dec	1955431H1	6800	7075
62	256009.2.dec	3699713H1	6694	6856	62	256009.2.dec	2265155H1	6801	7070
62	256009.2.dec	4824777H1	6694	6925	62	256009.2.dec	3352558H1	6801	7093
62	256009.2.dec	4407873H1	6694	6956	62	256009.2.dec	4242674H1	6800	6987
62	256009.2.dec	3706839H1	6696	6968	62	256009.2.dec	555446H1	6802	7043
62	256009.2.dec	663677H1	6696	6935	62	256009.2.dec	933491H1	6800	7072
62	256009.2.dec	1456470H1	6698	6972	62	256009.2.dec	2972455H2	6801	7098
62	256009.2.dec	968683H1	6703	6976	62	256009.2.dec	3726151H1	6802	6923
62	256009.2.dec	6221267H1	6704	6979	62	256009.2.dec	3369242H1	6802	7046
62	256009.2.dec	2099129H1	6706	6960	62	256009.2.dec	4880939H1	6802	7080
62	256009.2.dec	2429628H1	6706	6939	62	256009.2.dec	953686R1	6802	7215
62	256009.2.dec	895220R1	6707	7113	62	256009.2.dec	1445580H1	6802	7043
62	256009.2.dec	895220H1	6707	6926	62	256009.2.dec	2530970H1	6802	7032
62	256009.2.dec	2971992H1	6709	7001	62	256009.2.dec	2639476H1	6802	7050
62	256009.2.dec	2354602H1	6713	6935	62	256009.2.dec	953686H1	6802	7045
62	256009.2.dec	3441955H1	6713	6959	62	256009.2.dec	4507544H1	6802	7079
62	256009.2.dec	3704091H1	6713	6980	62	256009.2.dec	3726182H1	6802	7055
62	256009.2.dec	3705591H1	6714	6991	62	256009.2.dec	g1390836	6803	7209
62	256009.2.dec	3481169H1	6714	6854	62	256009.2.dec	4815838H1	6802	7057
62	256009.2.dec	2647507H1	6717	6971	62	256009.2.dec	2508350H1	6803	7057
62	256009.2.dec	2260986H1	6722	6943	62	256009.2.dec	2061029H1	6802	7061
62	256009.2.dec	2366005H1	6723	6956	62	256009.2.dec	2910492H1	6803	7052
62	256009.2.dec	344692H1	6730	6929	62	256009.2.dec	2061029R6	6802	7124
62	256009.2.dec	4629622H1	6730	6990	62	256009.2.dec	g5112634	6803	7218
62	256009.2.dec	4625565T6	6751	7201	62	256009.2.dec	3282530H1	6804	7046
62	256009.2.dec	4383604H1	6755	7001	62	256009.2.dec	4879137H1	5767	6051
62	256009.2.dec	385999H1	6763	7029	62	256009.2.dec	2579142H1	5789	6048
62	256009.2.dec	2913295H2	6764	7035	62	256009.2.dec	3286303H2	5797	6063
62	256009.2.dec	478883H1	6764	7049	62	256009.2.dec	3405455H1	5802	6041
62	256009.2.dec	3287375H1	6767	7010	62	256009.2.dec	6521704H1	5808	5885
62	256009.2.dec	6311868H1	6767	7230	62	256009.2.dec	1986283H1	5822	6032
62	256009.2.dec	2903120H1	6765	7068	62	256009.2.dec	2911956H1	5829	6113
62	256009.2.dec	6484690H1	6769	7215	62	256009.2.dec	1403913H1	5833	6084
62	256009.2.dec	1727418H1	6779	6987	62	256009.2.dec	5437246H1	5842	6082
62	256009.2.dec	4654772H1	6780	7027	62	256009.2.dec	6492553H1	5851	6377
62	256009.2.dec	666300H1	6787	6997	62	256009.2.dec	3025734H1	5852	6097
62	256009.2.dec	g921826	6789	7192	62	256009.2.dec	4456910H1	5865	6130
62	256009.2.dec	4351905H1	6788	6948	62	256009.2.dec	5093151H1	5870	6132
62	256009.2.dec	1596705H1	6789	7011	62	256009.2.dec	3423758H1	5871	6126
62	256009.2.dec	2998188H1	6789	7046	62	256009.2.dec	3761955H1	5880	6181
62	256009.2.dec	2998354H1	6789	7047	62	256009.2.dec	5301333H1	5882	6083
62	256009.2.dec	5450729H1	6789	7059	62	256009.2.dec	6380485H1	5882	6153
62	256009.2.dec	1406482H1	6789	7024	62	256009.2.dec	2842710H1	5882	6164
62	256009.2.dec	g864197	6793	7137	62	256009.2.dec	4138977H1	5885	6162
62	256009.2.dec	1880440H1	6794	7039	62	256009.2.dec	4353518H1	5887	6065
62	256009.2.dec	g995262	6795	7200	62	256009.2.dec	5048915H1	5897	6153
62	256009.2.dec	g1847140	6795	7184	62	256009.2.dec	4874435H1	5903	6170
62	256009.2.dec	5328912H1	6797	7039	62	256009.2.dec	2552601H1	5913	6166
62	256009.2.dec	g2005208	6798	7103	62	256009.2.dec	2970306H2	5921	6239
62	256009.2.dec	862304T1	6797	7167	62	256009.2.dec	2095611H1	5922	6188
62	256009.2.dec	4382949H1	6798	7052	62	256009.2.dec	2253545H1	5921	6158
62	256009.2.dec	1209525T1	6797	7174	62	256009.2.dec	3404668H1	5922	6161
62	256009.2.dec	545331H1	6796	7032	62	256009.2.dec	3886564H1	5927	6163
62	256009.2.dec	4070318H1	6801	6924	62	256009.2.dec	5550359H1	5929	6178
62	256009.2.dec	567575H1	6799	7058	62	256009.2.dec	366241H1	5930	6121
62	256009.2.dec	2180691H1	6799	7054	62	256009.2.dec	5173270H1	5948	6224
62	256009.2.dec	1559402H1	6799	7018	62	256009.2.dec	3281852H1	5965	6211
62	256009.2.dec	3487562H1	6799	7084	62	256009.2.dec	3678857H1	5980	6209
62	256009.2.dec	g5397606	6799	7217	62	256009.2.dec	3321667H1	5992	6276
62	256009.2.dec	5182883H1	6800	6959	62	256009.2.dec	2095264H1	5996	6272
62	256009.2.dec	5478393H1	6799	7079	62	256009.2.dec	4361881H1	5999	6249
62	256009.2.dec	933491R1	6800	7215	62	256009.2.dec	4357478H1	6014	6094

Table 4

62	256009.2.dec	3688656H1	6020	6310
62	256009.2.dec	2790077H2	6025	6309
62	256009.2.dec	552252H1	6038	6271
62	256009.2.dec	1601346F6	6038	6367
62	256009.2.dec	1601346H1	6038	6247
62	256009.2.dec	214224H1	6053	6232
62	256009.2.dec	5466354H1	6056	6319
62	256009.2.dec	4574252H1	6065	6322
62	256009.2.dec	5505467H1	6070	6309
62	256009.2.dec	6246193H1	6091	6605
62	256009.2.dec	4539817H1	6114	6250
62	256009.2.dec	6411666H1	6119	6560
62	256009.2.dec	6372383H1	6125	6313
62	256009.2.dec	427415H1	6138	6336
62	256009.2.dec	2121658H1	6152	6384
62	256009.2.dec	5333389H1	6152	6373
62	256009.2.dec	1726084H1	6153	6374
62	256009.2.dec	1726084F6	6153	6674
62	256009.2.dec	4291681H1	6154	6329
62	256009.2.dec	387731H1	6156	6384
62	256009.2.dec	446703H1	6156	6384
62	256009.2.dec	387605H1	6158	6384
62	256009.2.dec	4171129H1	6159	6384
62	256009.2.dec	712351H1	6166	6378
62	256009.2.dec	4895530H1	6168	6467
62	256009.2.dec	2840332H1	6169	6384
62	256009.2.dec	6493278H1	6178	6700
62	256009.2.dec	4608210H1	6185	6445
62	256009.2.dec	4325384H1	6195	6312
62	256009.2.dec	2879614H1	6197	6499
62	256009.2.dec	3884625H1	6203	6467
62	256009.2.dec	4355435H1	6206	6384
62	256009.2.dec	5136475H1	6208	6491
62	256009.2.dec	3724538H1	6214	6509
62	256009.2.dec	4881090H1	6217	6481
62	256009.2.dec	5134096H1	6231	6484
62	256009.2.dec	960344H1	6237	6384
62	256009.2.dec	3426474H1	6242	6509
62	256009.2.dec	g1634324	6254	6620
62	256009.2.dec	3682063H1	6255	6370
62	256009.2.dec	4150782H1	6262	6505
62	256009.2.dec	3774534H1	6263	6545
62	256009.2.dec	6409346H1	6264	6584
62	256009.2.dec	2611942H1	6285	6537
62	256009.2.dec	786520H1	6288	6498
62	256009.2.dec	4010059H1	6288	6559
62	256009.2.dec	965650H1	6295	6384
62	256009.2.dec	4327206H1	6301	6566
62	256009.2.dec	762834H1	6310	6491
62	256009.2.dec	3235055H1	6313	6560
62	256009.2.dec	3041143H1	6313	6570
62	256009.2.dec	1814602H1	6314	6558
62	256009.2.dec	4373041H1	6317	6385
62	256009.2.dec	5218032H1	6316	6573
62	256009.2.dec	5432981H1	6320	6522
62	256009.2.dec	5432864H1	6320	6524
62	256009.2.dec	4856094H1	6321	6571
62	256009.2.dec	1907445H1	6336	6568
62	256009.2.dec	2645473H1	6408	6653
62	256009.2.dec	424883H1	6411	6568
62	256009.2.dec	2225449H1	6411	6639
62	256009.2.dec	1456922H1	6411	6564
62	256009.2.dec	3047472H1	6411	6688
62	256009.2.dec	5069778H1	6411	6661
62	256009.2.dec	2855974H1	6411	6610
62	256009.2.dec	2102283H1	6411	6638
62	256009.2.dec	427953H1	6411	6565
62	256009.2.dec	3172462H1	6411	6614
62	256009.2.dec	425389H1	6411	6553
62	256009.2.dec	1334229H1	6411	6630
62	256009.2.dec	2187059H1	6411	6646
62	256009.2.dec	1450113H1	6411	6609
62	256009.2.dec	425476H1	6411	6562
62	256009.2.dec	4274885H1	6411	6606
62	256009.2.dec	455157H1	6411	6632
62	256009.2.dec	4359206H1	6420	6698
62	256009.2.dec	4181068H1	6422	6691
62	256009.2.dec	6325161H1	6424	6643
62	256009.2.dec	2310850H1	6424	6685
62	256009.2.dec	2672163H1	6430	6671
62	256009.2.dec	3984431H1	6433	6712
62	256009.2.dec	5175841H1	6434	6707
62	256009.2.dec	3740961H1	6436	6744
62	256009.2.dec	3528730H1	6437	6712
62	256009.2.dec	2250643H1	6439	6695
62	256009.2.dec	911369H1	6457	6580
62	256009.2.dec	2782975H1	6458	6717
62	256009.2.dec	g2156125	6454	6864
62	256009.2.dec	4645746H1	6459	6725
62	256009.2.dec	3790144H1	6462	6683
62	256009.2.dec	3098026H1	6464	6766
62	256009.2.dec	3786369H1	6464	6752
62	256009.2.dec	g2111938	6463	6898
62	256009.2.dec	4302140H1	6491	6732
62	256009.2.dec	3441270H1	6511	6751
62	256009.2.dec	g2207135	6510	7002
62	256009.2.dec	4881155H1	6519	6776
62	256009.2.dec	360503H1	2194	2455
62	256009.2.dec	g2356298	2458	2825
62	256009.2.dec	5059091H1	2496	2760
62	256009.2.dec	g178282	2535	6589
62	256009.2.dec	5629802H1	2775	2913
62	256009.2.dec	4778995H1	2765	3088
62	256009.2.dec	g2021107	2806	3052
62	256009.2.dec	1521307H1	2945	3137
62	256009.2.dec	1521719H1	2945	3115
62	256009.2.dec	2786057H1	2945	3189
62	256009.2.dec	6488485H1	3028	3528
62	256009.2.dec	5637372H1	3032	3280
62	256009.2.dec	5637260H1	3032	3294
62	256009.2.dec	5518962H1	3096	3354
62	256009.2.dec	4454257H1	3101	3275
62	256009.2.dec	5642023H1	3263	3497
62	256009.2.dec	1599061H1	3274	3482
62	256009.2.dec	5155543H1	3292	3557
62	256009.2.dec	6078401H1	3318	3615
62	256009.2.dec	5847863H1	3323	3578
62	256009.2.dec	5642649H1	3408	3666
62	256009.2.dec	5520057H1	3533	3803
62	256009.2.dec	5642541H1	3556	3787
62	256009.2.dec	3068454H1	3577	3894
62	256009.2.dec	3068454F6	3577	4018
62	256009.2.dec	6488494H1	3590	4142
62	256009.2.dec	3200011H1	3616	3894
62	256009.2.dec	6479761H1	3619	4153
62	256009.2.dec	2697253H1	3719	4021
62	256009.2.dec	5522487H1	3799	3892
62	256009.2.dec	5089970H1	3801	3971
62	256009.2.dec	6348817H1	3807	4089
62	256009.2.dec	1257838H1	3812	4062
62	256009.2.dec	5043875H1	3935	4190
62	256009.2.dec	960370H1	4046	4247
62	256009.2.dec	5438883H1	4065	4315
62	256009.2.dec	3600706H1	4135	4355

Table 4

62	256009.2.dec	3441916H1	4173	4434
62	256009.2.dec	5065557H2	4193	4446
62	256009.2.dec	6407410H1	4199	4494
62	256009.2.dec	5644707R8	4205	4599
62	256009.2.dec	3352414H1	4225	4337
62	256009.2.dec	6389610H1	4230	4378
62	256009.2.dec	5640341H1	4355	4601
62	256009.2.dec	2643454H1	4375	4621
62	256009.2.dec	3285115H1	4383	4619
62	256009.2.dec	3432281H1	4401	4635
62	256009.2.dec	6113754H1	4434	4655
62	256009.2.dec	2182372H1	4449	4704
62	256009.2.dec	3529034H1	4498	4802
62	256009.2.dec	6491824H1	4541	4783
62	256009.2.dec	6483681H1	4541	5017
62	256009.2.dec	2124605H1	4574	4874
62	256009.2.dec	2122823H1	4602	4882
62	256009.2.dec	3788796H1	4634	4909
62	256009.2.dec	5159083H1	4641	4795
62	256009.2.dec	g610938	4663	5048
62	256009.2.dec	1517151H1	4700	4896
62	256009.2.dec	4284867H1	4706	5020
62	256009.2.dec	6076896H1	4721	5013
62	256009.2.dec	4351039H1	4776	5046
62	256009.2.dec	2162143H1	4776	4941
62	256009.2.dec	4820360H1	4778	5045
62	256009.2.dec	3426167H1	4791	4910
62	256009.2.dec	5522528H1	4867	5123
62	256009.2.dec	3424683H1	4873	4958
62	256009.2.dec	2923879H1	4883	5148
62	256009.2.dec	g819017	4890	5068
62	256009.2.dec	1431243H1	4899	5143
62	256009.2.dec	6523601H1	4945	5442
62	256009.2.dec	3740282H1	4959	5248
62	256009.2.dec	3740282F6	4959	5255
62	256009.2.dec	2805285H1	4974	5257
62	256009.2.dec	3725454H1	4989	5263
62	256009.2.dec	3126237H1	5022	5297
62	256009.2.dec	198113H1	5034	5216
62	256009.2.dec	5088534H1	5057	5320
62	256009.2.dec	3379972H1	5061	5303
62	256009.2.dec	g707978	5088	5372
62	256009.2.dec	5344949H1	5097	5270
62	256009.2.dec	3423665H1	5108	5384
62	256009.2.dec	3095983H1	5112	5405
62	256009.2.dec	6490210H1	5138	5484
62	256009.2.dec	3761375H1	5154	5367
62	256009.2.dec	3394437H1	5161	5422
62	256009.2.dec	4519489H1	5182	5435
62	256009.2.dec	3200302H1	5208	5498
62	256009.2.dec	4353128H1	5222	5444
62	256009.2.dec	6485349H1	5249	5819
62	256009.2.dec	4324278H1	5256	5504
62	256009.2.dec	4788337H1	5265	5512
62	256009.2.dec	3424089H1	5265	5492
62	256009.2.dec	5201949H1	5290	5479
62	256009.2.dec	5136679H1	5302	5585
62	256009.2.dec	3740789H1	5330	5547
62	256009.2.dec	3360092H1	5356	5620
62	256009.2.dec	5349521H1	5364	5600
62	256009.2.dec	2399428H1	5373	5607
62	256009.2.dec	3227657H1	5381	5682
62	256009.2.dec	4459036H1	5383	5635
62	256009.2.dec	2844896H1	5406	5634
62	256009.2.dec	2845249H1	5406	5677
62	256009.2.dec	4949540H1	5412	5661
62	256009.2.dec	4923246H1	5426	5667
62	256009.2.dec	6077457H1	5478	5788
62	256009.2.dec	6077468H1	5479	5780
62	256009.2.dec	g625007	5478	5734
62	256009.2.dec	2631148H1	5481	5614
62	256009.2.dec	5638339H1	5486	5685
62	256009.2.dec	3203663H1	5509	5729
62	256009.2.dec	3209149H1	5525	5819
62	256009.2.dec	1673237H1	5546	5781
62	256009.2.dec	5043372H1	5552	5800
62	256009.2.dec	476250H1	5565	5817
62	256009.2.dec	6513254H1	5572	5833
62	256009.2.dec	5000485H1	5576	5838
62	256009.2.dec	4820523H1	5577	5863
62	256009.2.dec	2853117H1	5580	5851
62	256009.2.dec	5512281H1	5582	5818
62	256009.2.dec	899007H1	5585	5802
62	256009.2.dec	3425387H1	5588	5824
62	256009.2.dec	4902802H1	5629	5914
62	256009.2.dec	240687H1	5640	5819
62	256009.2.dec	5642467H1	5660	5918
62	256009.2.dec	4516914H1	5690	5942
62	256009.2.dec	5173253H1	5691	5967
62	256009.2.dec	3285110H1	5702	5938
62	256009.2.dec	4254424H1	5723	6000
62	256009.2.dec	5510107H1	5725	5956
62	256009.2.dec	2943137H1	5727	6029
62	256009.2.dec	1556574H1	5729	5934
62	256009.2.dec	1603021H1	5754	5956
62	256009.2.dec	g1522250	5759	5996
62	256009.2.dec	4624485H1	5766	6004
62	256009.2.dec	g2111876	6849	7223
62	256009.2.dec	g2718730	6849	7222
62	256009.2.dec	g1023224	6849	7119
62	256009.2.dec	849037R1	6849	7209
62	256009.2.dec	437146H1	6849	7059
62	256009.2.dec	4189371H1	6848	7204
62	256009.2.dec	918287H1	6849	7127
62	256009.2.dec	713272H1	6850	6932
62	256009.2.dec	g2584215	6850	7215
62	256009.2.dec	g3741328	6850	7216
62	256009.2.dec	2484109H1	6850	7178
62	256009.2.dec	g3232181	6851	7224
62	256009.2.dec	g663701	6852	7155
62	256009.2.dec	3836834H1	6853	7125
62	256009.2.dec	6552959H1	6858	7262
62	256009.2.dec	1973258H1	6860	7109
62	256009.2.dec	6372054H1	6861	7143
62	256009.2.dec	4907179H2	6863	7127
62	256009.2.dec	g3840340	6888	7219
62	256009.2.dec	214414H1	6863	7111
62	256009.2.dec	2718318H1	6864	7111
62	256009.2.dec	2803011H1	6864	7113
62	256009.2.dec	g2279342	6867	7215
62	256009.2.dec	g659626	6868	7219
62	256009.2.dec	611772H1	6868	7115
62	256009.2.dec	g4573987	6873	7215
62	256009.2.dec	g1679120	6874	7219
62	256009.2.dec	6296239H1	6874	7072
62	256009.2.dec	g5362892	6876	7223
62	256009.2.dec	g1390671	6876	7123
62	256009.2.dec	g5056412	6877	7214
62	256009.2.dec	g2821748	6877	7059
62	256009.2.dec	6408315H1	6879	7231
62	256009.2.dec	2584013H1	6879	7129
62	256009.2.dec	g5547977	6881	7215
62	256009.2.dec	4820791H1	6880	7149
62	256009.2.dec	2541637H1	6880	7108

Table 4

62	256009.2.dec	g5233772	6881	7220
62	256009.2.dec	g2002728	6882	7215
62	256009.2.dec	6403535H1	6884	7170
62	256009.2.dec	2757642H1	6884	7141
62	256009.2.dec	g3431012	6885	7215
62	256009.2.dec	2061029T6	6885	7175
62	256009.2.dec	1456470R1	6886	7215
62	256009.2.dec	g5547986	6887	7215
62	256009.2.dec	g4089043	6887	7219
62	256009.2.dec	2299044H1	6888	7123
62	256009.2.dec	231439F1	6889	7214
62	256009.2.dec	231439H1	6889	7056
62	256009.2.dec	g2194515	6890	7215
62	256009.2.dec	g4565079	6891	7215
62	256009.2.dec	2646878H1	6892	7149
62	256009.2.dec	g5152227	6893	7215
62	256009.2.dec	g3958452	6893	7215
62	256009.2.dec	4081731H1	6894	7181
62	256009.2.dec	916243H1	6896	7214
62	256009.2.dec	g3446745	6895	7223
62	256009.2.dec	916243T1	6896	7172
62	256009.2.dec	6566649H1	6900	7215
62	256009.2.dec	916243R1	6896	7214
62	256009.2.dec	g3016042	6897	7215
62	256009.2.dec	1844640H1	6897	7172
62	256009.2.dec	g1166675	6897	7336
62	256009.2.dec	g2224108	6897	7215
62	256009.2.dec	4370277H1	6898	7136
62	256009.2.dec	630279H1	6898	7147
62	256009.2.dec	4367694H1	6898	7145
62	256009.2.dec	6414051H1	6900	7222
62	256009.2.dec	4921996H1	6898	7168
62	256009.2.dec	3201114H1	6908	7187
62	256009.2.dec	148475H1	6909	7122
62	256009.2.dec	g4986417	6913	7215
62	256009.2.dec	g5037266	6917	7217
62	256009.2.dec	2295604H1	6917	7132
62	256009.2.dec	g995210	6925	7208
62	256009.2.dec	2909721H1	6925	7193
62	256009.2.dec	647214H1	6926	7178
62	256009.2.dec	1963727H1	6926	7208
62	256009.2.dec	5219907H1	6927	7178
62	256009.2.dec	2638578H1	6930	7168
62	256009.2.dec	6316385H1	6930	7218
62	256009.2.dec	796402F1	6930	7208
62	256009.2.dec	g4619637	6931	7214
62	256009.2.dec	544499H1	6933	7180
62	256009.2.dec	g4294531	6932	7215
62	256009.2.dec	791519H1	6936	7147
62	256009.2.dec	935673H1	6936	7187
62	256009.2.dec	2127078H1	6936	7206
62	256009.2.dec	g1424954	6940	7215
62	256009.2.dec	5286993H1	6937	7193
62	256009.2.dec	417350H1	6945	7009
62	256009.2.dec	3091273H1	6945	7154
62	256009.2.dec	1907434H1	6948	7187
62	256009.2.dec	355108H1	6949	7173
62	256009.2.dec	353642H1	6949	7189
62	256009.2.dec	6325058H1	6948	7211
62	256009.2.dec	2765275H1	6950	7184
62	256009.2.dec	6592881H1	6951	7215
62	256009.2.dec	g2021488	6954	7216
62	256009.2.dec	g5370352	6954	7214
62	256009.2.dec	3233506H1	6963	7200
62	256009.2.dec	2947006H2	6964	7215
62	256009.2.dec	3047916H1	6965	7216
62	256009.2.dec	g2402018	6972	7215
62	256009.2.dec	5339947H1	6972	7215
62	256009.2.dec	853197H1	6973	7215
62	256009.2.dec	g2211699	6974	7219
62	256009.2.dec	477163H1	6975	7213
62	256009.2.dec	3519575H1	6975	7216
62	256009.2.dec	571449H1	6975	7220
62	256009.2.dec	4418748H1	6975	7214
62	256009.2.dec	2024855H1	6982	7215
62	256009.2.dec	g1847139	6983	7215
62	256009.2.dec	g5635569	6987	7215
62	256009.2.dec	6219701H1	6989	7194
62	256009.2.dec	1998187H1	6992	7265
62	256009.2.dec	1297531H1	6996	7220
62	256009.2.dec	668356H1	6996	7212
62	256009.2.dec	1297531F1	6996	7215
62	256009.2.dec	2022823H1	6996	7215
62	256009.2.dec	936753H1	6996	7215
62	256009.2.dec	4764627H1	6997	7213
62	256009.2.dec	1251487H1	7000	7215
62	256009.2.dec	2047571H1	7000	7204
62	256009.2.dec	1251487F1	7000	7215
62	256009.2.dec	5054809H1	7002	7286
62	256009.2.dec	5056688H1	7002	7217
62	256009.2.dec	6483288H1	1	470
62	256009.2.dec	g4196104	362	769
62	256009.2.dec	5643206H1	425	684
62	256009.2.dec	g2264001	436	849
62	256009.2.dec	6487378H1	463	965
62	256009.2.dec	g4330828	485	734
62	256009.2.dec	4705323H1	541	794
62	256009.2.dec	3072025F6	600	886
62	256009.2.dec	3072025H1	601	891
62	256009.2.dec	5090601H1	642	921
62	256009.2.dec	2629979H1	647	890
62	256009.2.dec	g535176	650	2250
62	256009.2.dec	5642794H1	762	1011
62	256009.2.dec	6430548H1	909	1280
62	256009.2.dec	5637918H1	1012	1271
62	256009.2.dec	5868585H1	1118	1379
62	256009.2.dec	5631903H1	1120	1340
62	256009.2.dec	5042264H1	1147	1242
62	256009.2.dec	5641815H1	1226	1462
62	256009.2.dec	4285984H1	1240	1439
62	256009.2.dec	6492444H1	1375	1780
62	256009.2.dec	5637104H1	1429	1634
62	256009.2.dec	g2620140	1457	1713
62	256009.2.dec	g828506	1513	1713
62	256009.2.dec	5092421H1	1519	1784
62	256009.2.dec	5638723R8	1563	1844
62	256009.2.dec	5627419R8	1620	2020
62	256009.2.dec	5510689H1	1631	1854
62	256009.2.dec	5091905H1	1812	2100
62	256009.2.dec	g5674686	1878	2286
62	256009.2.dec	5640121H1	1915	2180
62	256009.2.dec	5090519H1	2033	2309
62	256009.2.dec	6492949H1	2050	2609
62	256009.2.dec	4165853H1	7002	7215
62	256009.2.dec	g1497138	7003	7215
62	256009.2.dec	2234013H1	7007	7215
62	256009.2.dec	3108980H1	7014	7207
62	256009.2.dec	1899702H1	7016	7220
62	256009.2.dec	g1023225	7019	7211
62	256009.2.dec	789178H1	7020	7202
62	256009.2.dec	1685886H1	7020	7215
62	256009.2.dec	789178R1	7020	7214
62	256009.2.dec	3410258H1	7022	7196
62	256009.2.dec	5996209H1	7024	7215

Table 4

62	256009.2.dec	g4088409	7033	7217	62	256009.2.dec	2544852H2	7136	7215
62	256009.2.dec	5701245H1	7033	7215	62	256009.2.dec	560899H1	7148	7215
62	256009.2.dec	2772612H1	7031	7214	62	256009.2.dec	2412770H1	7148	7215
62	256009.2.dec	1801172H1	7031	7197	62	256009.2.dec	3095646H1	7153	7225
62	256009.2.dec	2772426H1	7031	7220	62	256009.2.dec	2673970H1	7159	7215
62	256009.2.dec	1518474H1	7032	7215	62	256009.2.dec	4275683H1	7161	7215
62	256009.2.dec	1999308H1	7033	7215	63	231892.12.dec	2204333H1	60	316
62	256009.2.dec	3705212H1	7033	7215	63	231892.12.dec	3335919H1	60	311
62	256009.2.dec	971310H1	7033	7215	63	231892.12.dec	3270313H1	62	317
62	256009.2.dec	1679673H1	7035	7215	63	231892.12.dec	661159H1	60	333
62	256009.2.dec	g1492912	7039	7216	63	231892.12.dec	3153473H1	57	332
62	256009.2.dec	473713H1	7042	7215	63	231892.12.dec	g1924359	57	410
62	256009.2.dec	4081296H1	7044	7214	63	231892.12.dec	3748222H1	142	388
62	256009.2.dec	g4900868	7045	7215	63	231892.12.dec	2618557H1	142	344
62	256009.2.dec	723293R1	7047	7215	63	231892.12.dec	3576547H1	142	437
62	256009.2.dec	6360023H2	7047	7215	63	231892.12.dec	3423159H1	142	402
62	256009.2.dec	1257619H1	7053	7214	63	231892.12.dec	2705336H1	68	337
62	256009.2.dec	855352H1	7051	7217	63	231892.12.dec	3180333H1	61	385
62	256009.2.dec	3885147H1	7052	7214	63	231892.12.dec	2378646H1	66	295
62	256009.2.dec	2680924H1	7052	7215	63	231892.12.dec	g880445	74	395
62	256009.2.dec	g2251970	7054	7215	63	231892.12.dec	g2100238	101	521
62	256009.2.dec	3248338H1	7052	7215	63	231892.12.dec	g2719117	110	318
62	256009.2.dec	2701674H1	7053	7215	63	231892.12.dec	g1167090	99	319
62	256009.2.dec	277311H1	7056	7215	63	231892.12.dec	g3040712	1106	1582
62	256009.2.dec	g2195319	7056	7215	63	231892.12.dec	5208359H1	1107	1341
62	256009.2.dec	3433206H1	7056	7202	63	231892.12.dec	1989582H1	1107	1364
62	256009.2.dec	1680415H1	7058	7215	63	231892.12.dec	g2933999	1109	1583
62	256009.2.dec	768346H1	7058	7186	63	231892.12.dec	1850596F6	1113	1583
62	256009.2.dec	2252941H1	7058	7215	63	231892.12.dec	g4113786	1114	1583
62	256009.2.dec	4506553H1	7059	7215	63	231892.12.dec	g5396231	1121	1582
62	256009.2.dec	583974H1	7063	7215	63	231892.12.dec	g3049283	1123	1594
62	256009.2.dec	6372154H1	7063	7313	63	231892.12.dec	3809994H1	1124	1324
62	256009.2.dec	3706262H1	7064	7215	63	231892.12.dec	5151961H1	1126	1376
62	256009.2.dec	5303990H1	7066	7215	63	231892.12.dec	g3049285	1125	1602
62	256009.2.dec	1928975H1	7071	7215	63	231892.12.dec	g3593701	1126	1589
62	256009.2.dec	1955027H1	7072	7171	63	231892.12.dec	652419H1	1127	1263
62	256009.2.dec	833093H1	7072	7215	63	231892.12.dec	652839H1	1127	1385
62	256009.2.dec	6172447H1	7073	7214	63	231892.12.dec	3413937H1	937	1180
62	256009.2.dec	959475H1	7077	7167	63	231892.12.dec	538069R6	934	1440
62	256009.2.dec	2322503H1	7077	7215	63	231892.12.dec	1325071H1	942	1171
62	256009.2.dec	4186918H1	7078	7215	63	231892.12.dec	1732753H1	946	1131
62	256009.2.dec	2104727H1	7079	7216	63	231892.12.dec	1861768H1	944	1206
62	256009.2.dec	3016971H1	7086	7209	63	231892.12.dec	3601675H1	949	1243
62	256009.2.dec	2006146H1	7085	7214	63	231892.12.dec	5032777H1	1020	1282
62	256009.2.dec	3091710H1	7086	7216	63	231892.12.dec	3417428H1	1020	1255
62	256009.2.dec	4363543H1	7087	7183	63	231892.12.dec	4322516H1	1024	1279
62	256009.2.dec	3206917H1	7090	7220	63	231892.12.dec	2396782H1	1024	1215
62	256009.2.dec	551977H1	7087	7214	63	231892.12.dec	g2163696	1421	1590
62	256009.2.dec	g2243889	7105	7220	63	231892.12.dec	g4523144	1416	1583
62	256009.2.dec	4207320H1	7106	7221	63	231892.12.dec	6219253H1	1427	1583
62	256009.2.dec	g789052	7106	7167	63	231892.12.dec	g2558408	1406	1590
62	256009.2.dec	426912H1	7107	7252	63	231892.12.dec	1850596H1	1413	1587
62	256009.2.dec	6402354H1	7108	7215	63	231892.12.dec	g5176544	1414	1585
62	256009.2.dec	2784877H1	7109	7215	63	231892.12.dec	g5674817	1151	1583
62	256009.2.dec	2684285H1	7111	7216	63	231892.12.dec	2723201H1	1151	1415
62	256009.2.dec	g5367272	7121	7216	63	231892.12.dec	g2881444	1153	1376
62	256009.2.dec	5078648H1	7127	7212	63	231892.12.dec	4628729H1	1155	1405
62	256009.2.dec	769716H1	7126	7215	63	231892.12.dec	2008891H1	1155	1338
62	256009.2.dec	g2155990	7127	7220	63	231892.12.dec	g1968990	1156	1476
62	256009.2.dec	2662275F6	7127	7215	63	231892.12.dec	g4373423	1161	1583
62	256009.2.dec	757227H1	7127	7215	63	231892.12.dec	6571162H1	1157	1586
62	256009.2.dec	4508279H1	7127	7215	63	231892.12.dec	g3917275	1165	1585
62	256009.2.dec	1966145H1	7128	7219	63	231892.12.dec	1294451H1	1170	1381
62	256009.2.dec	2356529H1	7127	7215	63	231892.12.dec	g5632359	1170	1584
62	256009.2.dec	4187420H1	7132	7215	63	231892.12.dec	6114459H1	1171	1426
62	256009.2.dec	2648339H1	7128	7215	63	231892.12.dec	638561H1	1171	1443
62	256009.2.dec	5002755H1	7138	7227	63	231892.12.dec	638534H1	1171	1430

Table 4

63	231892.12.dec	g1138914	1172	1583
63	231892.12.dec	g4003828	1174	1587
63	231892.12.dec	g5446602	1175	1583
63	231892.12.dec	g4080829	1177	1592
63	231892.12.dec	g3777716	1180	1556
63	231892.12.dec	2410203H1	1181	1395
63	231892.12.dec	6350290H2	1182	1501
63	231892.12.dec	892507H1	1182	1445
63	231892.12.dec	g3110005	1182	1586
63	231892.12.dec	2009233H1	1188	1283
63	231892.12.dec	g4892874	1189	1583
63	231892.12.dec	g2884766	1191	1376
63	231892.12.dec	6426273H1	1192	1602
63	231892.12.dec	g3415976	1191	1587
63	231892.12.dec	g5631151	1194	1585
63	231892.12.dec	g2348544	1193	1584
63	231892.12.dec	2706868H1	1201	1483
63	231892.12.dec	1671991H1	1207	1422
63	231892.12.dec	4839470H1	1208	1465
63	231892.12.dec	g2945978	1207	1587
63	231892.12.dec	g4525143	1209	1584
63	231892.12.dec	g1152000	1328	1583
63	231892.12.dec	g3845862	1331	1584
63	231892.12.dec	2403166T6	1333	1545
63	231892.12.dec	4150694H1	1334	1583
63	231892.12.dec	5272824H1	1340	1583
63	231892.12.dec	g3086175	1337	1583
63	231892.12.dec	g2229832	1341	1580
63	231892.12.dec	g4270144	1345	1583
63	231892.12.dec	2126862H1	1351	1580
63	231892.12.dec	6356509H1	1290	1582
63	231892.12.dec	335774H1	1352	1583
63	231892.12.dec	605403H1	1357	1580
63	231892.12.dec	1881336T6	1358	1543
63	231892.12.dec	g3050327	1365	1590
63	231892.12.dec	g5591239	1368	1583
63	231892.12.dec	g5591232	1369	1583
63	231892.12.dec	g3959585	1372	1591
63	231892.12.dec	g2229948	1374	1583
63	231892.12.dec	g2898260	1291	1585
63	231892.12.dec	g651121	1378	1563
63	231892.12.dec	g2115189	1382	1586
63	231892.12.dec	g1124380	1293	1585
63	231892.12.dec	g708377	1388	1589
63	231892.12.dec	3344031H1	1392	1580
63	231892.12.dec	g3839206	1292	1595
63	231892.12.dec	g2229771	1394	1584
63	231892.12.dec	g2877306	1398	1583
63	231892.12.dec	546963H1	1292	1571
63	231892.12.dec	g4452672	1295	1583
63	231892.12.dec	g1148108	1296	1589
63	231892.12.dec	627862H1	1401	1583
63	231892.12.dec	g1833004	1298	1586
63	231892.12.dec	2921838H1	1298	1569
63	231892.12.dec	g1201653	1298	1584
63	231892.12.dec	g2054698	1301	1583
63	231892.12.dec	g1644781	1301	1607
63	231892.12.dec	5048046R6	1307	1582
63	231892.12.dec	2880459H1	1312	1583
63	231892.12.dec	g1628778	1312	1594
63	231892.12.dec	g1161956	1316	1588
63	231892.12.dec	g2163878	1316	1583
63	231892.12.dec	g3803279	1316	1583
63	231892.12.dec	g3213517	1320	1588
63	231892.12.dec	3537729H1	30	198
63	231892.12.dec	1466792H1	32	206
63	231892.12.dec	g1920921	40	492
63	231892.12.dec	3598237H1	52	349
63	231892.12.dec	2458456H1	53	292
63	231892.12.dec	3394221H1	53	331
63	231892.12.dec	3052244H1	53	331
63	231892.12.dec	2137522H1	54	289
63	231892.12.dec	3115206H1	55	292
63	231892.12.dec	1892023H1	55	302
63	231892.12.dec	2457265H1	53	304
63	231892.12.dec	3126695H2	55	353
63	231892.12.dec	g2715524	1208	1588
63	231892.12.dec	g3203893	1209	1583
63	231892.12.dec	588058H1	1213	1483
63	231892.12.dec	g5364810	1214	1596
63	231892.12.dec	g3934453	1213	1591
63	231892.12.dec	g5633690	1213	1585
63	231892.12.dec	g5670959	1214	1583
63	231892.12.dec	g4112640	1129	1583
63	231892.12.dec	g3446656	1131	1587
63	231892.12.dec	g3918133	1135	1589
63	231892.12.dec	1385090H1	1134	1374
63	231892.12.dec	4087769H1	1134	1404
63	231892.12.dec	1469989T6	1136	1546
63	231892.12.dec	g4523247	1135	1583
63	231892.12.dec	g3031143	1134	1583
63	231892.12.dec	g4267211	1134	1583
63	231892.12.dec	5095945H2	1138	1397
63	231892.12.dec	g3238357	1139	1589
63	231892.12.dec	g4390111	1141	1590
63	231892.12.dec	g4077508	1140	1368
63	231892.12.dec	4515238H1	1147	1404
63	231892.12.dec	g2229837	1147	1551
63	231892.12.dec	g3330195	1150	1583
63	231892.12.dec	2818513H1	249	475
63	231892.12.dec	2455113H1	251	495
63	231892.12.dec	3537402H1	257	491
63	231892.12.dec	3537450H1	257	548
63	231892.12.dec	3365926H1	259	491
63	231892.12.dec	713333H1	259	485
63	231892.12.dec	2444890H1	259	474
63	231892.12.dec	g2165426	256	681
63	231892.12.dec	712519H1	260	317
63	231892.12.dec	5941877H1	262	409
63	231892.12.dec	3341189H1	270	528
63	231892.12.dec	2849094H1	272	527
63	231892.12.dec	3503142H1	273	555
63	231892.12.dec	1565396H1	277	483
63	231892.12.dec	3762075H1	278	564
63	231892.12.dec	1418549H1	279	453
63	231892.12.dec	1418090H1	279	528
63	231892.12.dec	1881336F6	281	712
63	231892.12.dec	1418926H1	692	926
63	231892.12.dec	g2558192	692	778
63	231892.12.dec	1647830H1	698	899
63	231892.12.dec	2746136H1	699	933
63	231892.12.dec	1299324H1	700	921
63	231892.12.dec	880929H1	778	896
63	231892.12.dec	g2163948	786	1137
63	231892.12.dec	2901409H1	863	1167
63	231892.12.dec	2458906H1	380	598
63	231892.12.dec	5908231H1	386	584
63	231892.12.dec	2662336H1	387	620
63	231892.12.dec	3800385H1	390	651
63	231892.12.dec	g1616396	394	663
63	231892.12.dec	2637438H1	405	638
63	231892.12.dec	4910861H2	426	687
63	231892.12.dec	863497H1	426	675
63	231892.12.dec	1959872H1	429	697

Table 4

63	231892.12.dec	2779339H1	432	678
63	231892.12.dec	2925313H1	456	725
63	231892.12.dec	1271944H1	464	708
63	231892.12.dec	1232955H1	464	685
63	231892.12.dec	3223737H1	469	777
63	231892.12.dec	1484712H1	478	638
63	231892.12.dec	3695508H1	493	774
63	231892.12.dec	3500611H1	493	773
63	231892.12.dec	3349768H1	499	765
63	231892.12.dec	1674505H1	502	714
63	231892.12.dec	2382249H1	559	791
63	231892.12.dec	1375225H1	587	842
63	231892.12.dec	1375225F6	587	758
63	231892.12.dec	3190172H1	635	950
63	231892.12.dec	1574338H1	639	849
63	231892.12.dec	g1189551	667	917
63	231892.12.dec	2844332H1	670	940
63	231892.12.dec	402145H1	690	926
63	231892.12.dec	3753514H1	314	616
63	231892.12.dec	2557616H1	323	595
63	231892.12.dec	1341814H1	323	519
63	231892.12.dec	731683R1	323	669
63	231892.12.dec	g708378	326	660
63	231892.12.dec	g2115395	335	628
63	231892.12.dec	2545989H1	348	530
63	231892.12.dec	2403449H1	348	569
63	231892.12.dec	2779994H1	349	600
63	231892.12.dec	5285550H1	349	461
63	231892.12.dec	2771977H1	353	599
63	231892.12.dec	2286386H1	359	596
63	231892.12.dec	2058238H1	363	600
63	231892.12.dec	3189574H1	364	660
63	231892.12.dec	g1727293	371	486
63	231892.12.dec	g1774709	371	558
63	231892.12.dec	2692980H1	374	636
63	231892.12.dec	g2100130	1	209
63	231892.12.dec	6301221H1	1	116
63	231892.12.dec	3576472H1	5	293
63	231892.12.dec	2403166H1	4	114
63	231892.12.dec	1870381H1	6	141
63	231892.12.dec	1804755H1	10	237
63	231892.12.dec	6606210H1	1	380
63	231892.12.dec	g2353927	1281	1583
63	231892.12.dec	g4687116	1282	1583
63	231892.12.dec	g4990332	1283	1583
63	231892.12.dec	g3277437	1284	1588
63	231892.12.dec	g2725785	1286	1583
63	231892.12.dec	g4004820	1286	1588
63	231892.12.dec	g1736316	1288	1592
63	231892.12.dec	g1733403	1287	1591
63	231892.12.dec	g4070065	1288	1583
63	231892.12.dec	g2910317	1280	1376
63	231892.12.dec	g4194161	1288	1587
63	231892.12.dec	g2321061	1288	1558
63	231892.12.dec	g4308757	1289	1584
63	231892.12.dec	g5233103	1283	1591
63	231892.12.dec	g2726125	1289	1583
63	231892.12.dec	1311118H1	1406	1583
63	231892.12.dec	2245159H1	1406	1583
63	231892.12.dec	387055H1	1407	1580
63	231892.12.dec	g4285750	1434	1586
63	231892.12.dec	g4394615	1440	1583
63	231892.12.dec	g4150176	1440	1587
63	231892.12.dec	g1271257	1449	1594
63	231892.12.dec	983370H1	1455	1583
63	231892.12.dec	983370T1	1455	1543
63	231892.12.dec	g3037378	1461	1584
63	231892.12.dec	g3038947	1466	1583
63	231892.12.dec	g2411416	1469	1585
63	231892.12.dec	g4874602	1471	1588
63	231892.12.dec	g3148716	1475	1583
63	231892.12.dec	g3042883	1474	1583
63	231892.12.dec	3745735H1	1477	1631
63	231892.12.dec	g3110113	1479	1584
63	231892.12.dec	g3039527	1483	1587
63	231892.12.dec	3590479H1	1489	1584
63	231892.12.dec	6028077H1	1497	1583
63	231892.12.dec	g1696451	1508	1588
63	231892.12.dec	g2251530	1515	1582
63	231892.12.dec	g4389717	1520	1583
63	231892.12.dec	g3055876	1521	1583
63	231892.12.dec	1881336H1	281	497
63	231892.12.dec	1730571H1	283	531
63	231892.12.dec	3585953H1	285	501
63	231892.12.dec	3336679H1	286	535
63	231892.12.dec	3602419H1	294	555
63	231892.12.dec	2053611H1	313	572
63	231892.12.dec	2050642H1	1214	1457
63	231892.12.dec	g4076833	1214	1583
63	231892.12.dec	g3433968	1214	1588
63	231892.12.dec	g1920922	1215	1583
63	231892.12.dec	g4264197	1216	1583
63	231892.12.dec	g5676296	1217	1588
63	231892.12.dec	g4243864	1220	1583
63	231892.12.dec	g3895704	1219	1583
63	231892.12.dec	g5554320	1220	1535
63	231892.12.dec	g3917870	1225	1584
63	231892.12.dec	g3644268	1226	1583
63	231892.12.dec	g4269820	1227	1583
63	231892.12.dec	1375225T6	1227	1543
63	231892.12.dec	g4084882	1227	1586
63	231892.12.dec	347608H1	1230	1468
63	231892.12.dec	g4649732	1232	1590
63	231892.12.dec	g3869737	1235	1583
63	231892.12.dec	1638737H1	1237	1411
63	231892.12.dec	g2754388	1238	1587
63	231892.12.dec	1636071H1	1237	1464
63	231892.12.dec	919225H1	863	1143
63	231892.12.dec	3571728H1	868	1139
63	231892.12.dec	g651120	868	1151
63	231892.12.dec	3766854H1	872	1173
63	231892.12.dec	1560301H1	885	1089
63	231892.12.dec	869717H1	887	1140
63	231892.12.dec	818102H1	905	1139
63	231892.12.dec	2018418H1	911	1167
63	231892.12.dec	1651958H1	912	1145
63	231892.12.dec	2937249H1	912	1199
63	231892.12.dec	2940340H1	912	1178
63	231892.12.dec	2955448H1	913	1144
63	231892.12.dec	2955448F6	913	1343
63	231892.12.dec	1475472H1	918	1098
63	231892.12.dec	1751019H1	921	1124
63	231892.12.dec	2568696H1	926	1145
63	231892.12.dec	2568515H1	926	1190
63	231892.12.dec	1319388H1	926	1150
63	231892.12.dec	4860284H1	1067	1336
63	231892.12.dec	406011H1	1068	1283
63	231892.12.dec	6411241H1	1068	1340
63	231892.12.dec	542412H1	1069	1314
63	231892.12.dec	817008H1	1075	1347
63	231892.12.dec	2953359T6	1078	1576
63	231892.12.dec	987383H1	1086	1395
63	231892.12.dec	g2899974	1090	1575
63	231892.12.dec	4467971H1	1093	1324

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63	231892.12.dec	540418H1	1093	1335
63	231892.12.dec	6160336H1	1096	1367
63	231892.12.dec	g1349663	1098	1579
63	231892.12.dec	3391333H1	1100	1326
63	231892.12.dec	g1289604	1107	1590
63	231892.12.dec	g5178166	1102	1584
63	231892.12.dec	1886761H1	1105	1369
63	231892.12.dec	1878271H1	1024	1294
63	231892.12.dec	3188440H1	1035	1281
63	231892.12.dec	1736789H1	1034	1225
63	231892.12.dec	1557363H1	1035	1197
63	231892.12.dec	1850596T6	1036	1546
63	231892.12.dec	1853066H1	1035	1264
63	231892.12.dec	633615H1	1035	1227
63	231892.12.dec	1735065H1	1035	1218
63	231892.12.dec	2650227H1	1035	1229
63	231892.12.dec	2650258H1	1035	1240
63	231892.12.dec	4596520H1	1035	1261
63	231892.12.dec	3540242H1	1035	1269
63	231892.12.dec	2759310H1	1035	1234
63	231892.12.dec	5186822H1	1039	1203
63	231892.12.dec	2989463T6	1040	1546
63	231892.12.dec	3801691H1	1042	1341
63	231892.12.dec	3802491H1	1042	1380
63	231892.12.dec	3089740H1	1047	1322
63	231892.12.dec	5340828H1	1048	1325
63	231892.12.dec	3128579H1	1048	1340
63	231892.12.dec	349802H1	1051	1317
63	231892.12.dec	1469950H1	1055	1155
63	231892.12.dec	5605748H1	1057	1297
63	231892.12.dec	4244841H1	1057	1310
63	231892.12.dec	351340H1	1060	1179
63	231892.12.dec	1977654H1	1059	1338
63	231892.12.dec	1418488H1	1432	1580
63	231892.12.dec	3575324H1	59	350
63	231892.12.dec	3437716H1	57	298
63	231892.12.dec	2696837H1	56	354
63	231892.12.dec	1892118H1	56	289
63	231892.12.dec	3347754H1	54	299
63	231892.12.dec	2264065H1	55	316
63	231892.12.dec	1478070H1	54	314
63	231892.12.dec	3082709H1	56	351
63	231892.12.dec	1341563H1	56	278
63	231892.12.dec	1855681H1	56	326
63	231892.12.dec	2526504H1	56	287
63	231892.12.dec	5043567H2	57	316
63	231892.12.dec	2463905H1	57	300
63	231892.12.dec	3077148H1	57	320
63	231892.12.dec	3239038H1	57	299
63	231892.12.dec	6497218H1	57	502
63	231892.12.dec	3122810H1	54	388
63	231892.12.dec	2434043H1	60	282
63	231892.12.dec	3078474H1	57	358
63	231892.12.dec	1859775H1	56	115
63	231892.12.dec	2467634H1	60	288
63	231892.12.dec	1393338H1	59	314
63	231892.12.dec	1711695H1	59	278
63	231892.12.dec	2991815H1	56	322
63	231892.12.dec	1317933H1	57	303
63	231892.12.dec	661199H1	60	320
63	231892.12.dec	1395795H1	59	268
63	231892.12.dec	2526346H1	56	303
63	231892.12.dec	3245594H1	61	311
63	231892.12.dec	1959645H1	57	301
63	231892.12.dec	3362542H1	142	360
63	231892.12.dec	1843501H1	142	370
63	231892.12.dec	2700956H1	142	384
63	231892.12.dec	2617909H1	142	355
63	231892.12.dec	6385750H1	145	430
63	231892.12.dec	g2240872	156	399
63	231892.12.dec	3180671H1	163	436
63	231892.12.dec	3255568H1	169	421
63	231892.12.dec	1785058H1	176	268
63	231892.12.dec	3455258H1	182	463
63	231892.12.dec	g3334898	182	1583
63	231892.12.dec	2846213H1	187	448
63	231892.12.dec	1532971H1	189	398
63	231892.12.dec	g1203619	191	520
63	231892.12.dec	g847234	195	428
63	231892.12.dec	878859H1	200	452
63	231892.12.dec	g1697121	196	562
63	231892.12.dec	2291868H1	200	385
63	231892.12.dec	2615766H1	208	484
63	231892.12.dec	4440531H1	216	410
63	231892.12.dec	g1733402	224	342
63	231892.12.dec	6169874H1	229	408
63	231892.12.dec	1444781H1	230	445
63	231892.12.dec	3563740H1	238	518
63	231892.12.dec	5678361H1	239	417
63	231892.12.dec	2484857H1	241	484
63	231892.12.dec	855867H1	248	469
63	231892.12.dec	5626936H1	248	450
63	231892.12.dec	g1303150	248	560
63	231892.12.dec	g4175728	1239	1589
63	231892.12.dec	g2659270	1238	1376
63	231892.12.dec	g4113163	1239	1586
63	231892.12.dec	6296673H1	1241	1542
63	231892.12.dec	g4194287	1241	1587
63	231892.12.dec	g3399839	1246	1583
63	231892.12.dec	1958239H1	1249	1507
63	231892.12.dec	4671164H1	1249	1512
63	231892.12.dec	g3428911	1249	1405
63	231892.12.dec	1927463H1	1249	1368
63	231892.12.dec	g1616285	1250	1488
63	231892.12.dec	g3918480	1251	1587
63	231892.12.dec	g3279206	1254	1590
63	231892.12.dec	4551689H1	1255	1474
63	231892.12.dec	g2784478	1254	1376
63	231892.12.dec	2426256H1	1255	1493
63	231892.12.dec	g3694470	1257	1586
63	231892.12.dec	g826517	1264	1592
63	231892.12.dec	g3000871	1264	1582
63	231892.12.dec	g4599945	1264	1582
63	231892.12.dec	2827756H1	1266	1546
63	231892.12.dec	5854044H1	1266	1528
63	231892.12.dec	g4391003	1267	1583
63	231892.12.dec	1364761H1	1269	1516
63	231892.12.dec	2017403H1	1272	1422
63	231892.12.dec	g4890638	1272	1587
63	231892.12.dec	g3883945	1273	1376
63	231892.12.dec	3876771H1	1273	1562
63	231892.12.dec	g517972	1281	1592
63	231892.12.dec	g4628861	1275	1586
63	231892.12.dec	g2788430	1277	1376
63	231892.12.dec	g2062988	1276	1587
63	231892.12.dec	6009646H1	1280	1553
63	231892.12.dec	g2768816	1279	1586
64	197445.1.oct	3493649H1	1829	1955
64	197445.1.oct	g3870474	1879	2330
64	197445.1.oct	g3840082	1879	2324
64	197445.1.oct	g4311546	1883	2329
64	197445.1.oct	g2210698	1885	2356
64	197445.1.oct	3254759H1	1892	2154
64	197445.1.oct	4632923H1	1331	1601

Table 4

64	197445.1.oct	3721127H1	1342	1645	64	197445.1.oct	2216768H1	1791	1955
64	197445.1.oct	2600188H1	1374	1534	64	197445.1.oct	1285672H1	1806	1944
64	197445.1.oct	776569H1	1440	1682	64	197445.1.oct	2958707H1	1517	1755
64	197445.1.oct	4213103H1	1255	1513	64	197445.1.oct	g1779556	1554	1964
64	197445.1.oct	2286618H1	1268	1500	64	197445.1.oct	5579394H1	1563	1785
64	197445.1.oct	5743342H1	1302	1574	64	197445.1.oct	463695T6	1571	1918
64	197445.1.oct	g4307960	1	483	64	197445.1.oct	1546362H1	1603	1805
64	197445.1.oct	g4243527	1	495	64	197445.1.oct	5076525H1	1225	1498
64	197445.1.oct	g4186422	1	486	64	197445.1.oct	4163716H1	1232	1503
64	197445.1.oct	g4074327	1	507	64	197445.1.oct	g3034044	1239	1307
64	197445.1.oct	3810949H1	1048	1239	64	197445.1.oct	5075231H1	1252	1427
64	197445.1.oct	1517215H1	1613	1789	64	197445.1.oct	4158314H1	1645	1888
64	197445.1.oct	g4452855	1640	1955	64	197445.1.oct	2201582H1	1651	1882
64	197445.1.oct	4158512H1	1645	1909	64	197445.1.oct	g2583246	1673	1961
64	197445.1.oct	4158413H1	1645	1867	64	197445.1.oct	5897546H1	1460	1755
64	197445.1.oct	1686311F6	1998	2326	64	197445.1.oct	g2539095	1487	1963
64	197445.1.oct	5519702H1	202	427	64	197445.1.oct	1833214H1	1502	1772
64	197445.1.oct	g3917499	19	484	64	197445.1.oct	g3538527	1512	1959
64	197445.1.oct	g1069368	64	381	64	197445.1.oct	2440656H1	1674	1927
64	197445.1.oct	3383583H1	100	215	64	197445.1.oct	1353593T6	1677	1916
64	197445.1.oct	1590911H1	104	306	64	197445.1.oct	g779497	1679	1864
64	197445.1.oct	g1810091	155	400	64	197445.1.oct	1353593H1	1684	1940
64	197445.1.oct	g1313174	158	552	64	197445.1.oct	1353593F6	1684	1959
64	197445.1.oct	709779H1	192	434	64	197445.1.oct	1353593F1	1684	1959
64	197445.1.oct	g1383698	218	551	64	197445.1.oct	4907774H1	1710	1967
64	197445.1.oct	g3743490	269	455	64	197445.1.oct	2659172H1	915	1155
64	197445.1.oct	g4078298	1	455	64	197445.1.oct	463695R6	916	1268
64	197445.1.oct	g3888019	1	453	64	197445.1.oct	463695H1	916	1160
64	197445.1.oct	1833139T6	1808	2281	64	197445.1.oct	g2874288	918	1307
64	197445.1.oct	1287809F1	1809	2321	64	197445.1.oct	4215357H1	919	1207
64	197445.1.oct	3790190H1	1910	2195	64	197445.1.oct	4841176H1	1012	1273
64	197445.1.oct	g1366863	1932	2349	64	197445.1.oct	g2819160	1034	1238
64	197445.1.oct	g3837964	1964	2323	64	197445.1.oct	g3837611	1	498
64	197445.1.oct	g2211068	1975	2356	64	197445.1.oct	g3834905	1	464
64	197445.1.oct	g3108713	1981	2340	64	197445.1.oct	g4085770	1	408
64	197445.1.oct	054382H1	1986	2183	64	197445.1.oct	g3841825	1	454
64	197445.1.oct	1686311T6	1991	2289	64	197445.1.oct	g3838085	1	463
64	197445.1.oct	1683894H1	1998	2221	64	197445.1.oct	g3917812	1	477
64	197445.1.oct	3152839H1	552	834	64	197445.1.oct	1833139H1	754	1009
64	197445.1.oct	5084942H1	564	814	64	197445.1.oct	g2114631	769	1231
64	197445.1.oct	3627622H1	579	882	64	197445.1.oct	g3803455	831	1230
64	197445.1.oct	5657362H1	635	878	64	197445.1.oct	g1350319	882	1447
64	197445.1.oct	g2114928	704	1107	64	197445.1.oct	g1954291	889	1209
64	197445.1.oct	g2167371	706	1212	64	197445.1.oct	3334792H1	898	1059
64	197445.1.oct	g2210757	722	1166	64	197445.1.oct	3810949F6	1046	1481
64	197445.1.oct	g2210776	722	1167	64	197445.1.oct	2915878H1	1075	1260
64	197445.1.oct	1833139R6	754	1217	64	197445.1.oct	665838H1	1154	1301
64	197445.1.oct	4694156H1	1514	1761	64	197445.1.oct	000077H1	1162	1635
64	197445.1.oct	4694145H1	1514	1762	64	197445.1.oct	4750730H1	1170	1413
64	197445.1.oct	5289647H1	2272	2531	64	197445.1.oct	2101538H1	1208	1437
64	197445.1.oct	g2575310	2367	2718	64	197445.1.oct	4334028H1	1207	1472
64	197445.1.oct	193222T6	2216	2279	64	197445.1.oct	g1069422	285	571
64	197445.1.oct	g1209957	2228	2631	64	197445.1.oct	g1382633	328	537
64	197445.1.oct	g2742820	2263	2326	64	197445.1.oct	g2188701	408	799
64	197445.1.oct	g2185069	1998	2329	64	197445.1.oct	368533H1	453	612
64	197445.1.oct	1686311H1	1998	2211	64	197445.1.oct	193222H1	467	669
64	197445.1.oct	1458660H1	2024	2301	64	197445.1.oct	5089936H1	538	711
64	197445.1.oct	2507791H1	2037	2266	64	197445.1.oct	g1241975	548	746
64	197445.1.oct	2293052H1	2048	2314	65	348775.1.oct	5273123H1	1	260
64	197445.1.oct	2450647H1	2048	2129	65	348775.1.oct	g4457572	1	254
64	197445.1.oct	1287809H1	2080	2321	65	348775.1.oct	4247889H1	10	269
64	197445.1.oct	2767430H1	2083	2320	65	348775.1.oct	4247889F6	10	350
64	197445.1.oct	1288563H1	2085	2321	65	348775.1.oct	4314064F6	18	243
64	197445.1.oct	g3173735	2106	2320	65	348775.1.oct	4314064H1	18	247
64	197445.1.oct	g1614963	2143	2318	65	348775.1.oct	4249504R6	34	233
64	197445.1.oct	5113750H1	1715	1985	65	348775.1.oct	2020732H1	62	170
64	197445.1.oct	g2825974	1736	1960	65	348775.1.oct	144037H1	72	380

Table 4

65	348775.1.oct	g274251	71	372
65	348775.1.oct	g1977679	80	397
65	348775.1.oct	3050367H1	107	237
65	348775.1.oct	1256650F6	118	624
65	348775.1.oct	3872405F6	131	544
65	348775.1.oct	2855002H1	145	217
65	348775.1.oct	g1400673	169	278
65	348775.1.oct	g1152145	169	572
65	348775.1.oct	g2261947	179	605
65	348775.1.oct	g3202759	185	567
65	348775.1.oct	g3401799	187	619
65	348775.1.oct	3872405H1	188	237
65	348775.1.oct	g1080465	188	500
65	348775.1.oct	g1212614	188	614
65	348775.1.oct	g1152143	242	572
65	348775.1.oct	5280125H1	321	571
65	348775.1.oct	3872405T6	409	641
65	348775.1.oct	3144983R6	464	830
65	348775.1.oct	g656518	472	792
65	348775.1.oct	3144983T6	502	830
65	348775.1.oct	4540767H1	517	625
65	348775.1.oct	3144983H1	532	830
65	348775.1.oct	g1080557	657	983
65	348775.1.oct	g656605	677	921
65	348775.1.oct	667904R6	801	1177
65	348775.1.oct	667211H1	801	1018
65	348775.1.oct	667904H1	801	983
65	348775.1.oct	2122331H1	858	1132
65	348775.1.oct	2122331F6	858	1296
65	348775.1.oct	667904T6	918	1181
65	348775.1.oct	2122331T6	1039	1601
65	348775.1.oct	2851162H1	1071	1330
65	348775.1.oct	g1238775	1087	1410
65	348775.1.oct	g1025865	1094	1360
65	348775.1.oct	5834437H1	1139	1387
65	348775.1.oct	g3367287	1315	1640
66	336239.5.dec	g3051635	1261	1629
66	336239.5.dec	5470996H1	1266	1442
66	336239.5.dec	1270035F1	1305	1629
66	336239.5.dec	1270035H1	1305	1563
66	336239.5.dec	2663702H1	1309	1486
66	336239.5.dec	g3861735	1327	1631
66	336239.5.dec	6141686H1	1340	1629
66	336239.5.dec	3574537H1	1	284
66	336239.5.dec	2477405H1	29	257
66	336239.5.dec	2861426H1	57	329
66	336239.5.dec	2861426F6	57	181
66	336239.5.dec	g1623654	55	390
66	336239.5.dec	3029277H1	64	359
66	336239.5.dec	2388525H1	107	323
66	336239.5.dec	2276938H1	107	311
66	336239.5.dec	g1957295	210	607
66	336239.5.dec	2915502F6	224	736
66	336239.5.dec	g2204397	1341	1634
66	336239.5.dec	2915502H1	224	507
66	336239.5.dec	616538R6	265	847
66	336239.5.dec	616538H1	265	562
66	336239.5.dec	6377253H1	265	544
66	336239.5.dec	g2350584	1369	1629
66	.336239.5.dec	616538T6	281	922
66	336239.5.dec	g2079319	300	603
66	336239.5.dec	2968881H1	1369	1655
66	336239.5.dec	g1614213	316	655
66	336239.5.dec	g2015301	364	613
66	336239.5.dec	4373981H1	400	659
66	336239.5.dec	3117904H1	1398	1678
66	336239.5.dec	4120062H1	411	666
66	336239.5.dec	5192237H1	1420	1532
66	336239.5.dec	g5441351	443	531
66	336239.5.dec	5169837H1	1420	1548
66	336239.5.dec	2520827H1	450	655
66	336239.5.dec	1544946H1	459	652
66	336239.5.dec	4182131H1	465	755
66	336239.5.dec	2646187H1	466	701
66	336239.5.dec	5608246H1	471	629
66	336239.5.dec	3171008H1	476	759
66	336239.5.dec	g4664883	494	950
66	336239.5.dec	g2112500	512	927
66	336239.5.dec	g3214688	566	959
66	336239.5.dec	2661626H1	575	808
66	336239.5.dec	044432H1	597	910
66	336239.5.dec	g3849291	598	963
66	336239.5.dec	5218272H1	603	831
66	336239.5.dec	3735235H1	634	894
66	336239.5.dec	4130911H2	657	911
66	336239.5.dec	2306365H1	659	878
66	336239.5.dec	g1966688	670	1079
66	336239.5.dec	2915502T6	701	920
66	336239.5.dec	g1577965	928	1294
66	336239.5.dec	g4109343	1003	1396
66	336239.5.dec	5222952T6	1059	1613
66	336239.5.dec	4919185H1	1065	1318
66	336239.5.dec	354404H1	1132	1471
66	336239.5.dec	g2874782	1159	1393
66	336239.5.dec	5431484H1	1166	1389
66	336239.5.dec	2319558H1	1176	1313
66	336239.5.dec	1450614H1	1189	1440
66	336239.5.dec	g5366948	1220	1639
66	336239.5.dec	g1963150	1228	1613
66	336239.5.dec	2364195H1	1247	1444
66	336239.5.dec	4030903H1	1450	1719
66	336239.5.dec	2056165H1	1457	1699
66	336239.5.dec	2873622H1	1487	1761
66	336239.5.dec	2884714H1	1495	1760
66	336239.5.dec	g2179137	1506	1932
66	336239.5.dec	5665189H1	1546	1784
66	336239.5.dec	g789870	1592	1821
66	336239.5.dec	3957532H2	1597	1892
66	336239.5.dec	680626H1	1594	1831
66	336239.5.dec	6367040H1	1637	1993
66	336239.5.dec	g1860417	1642	2022
66	336239.5.dec	g896896	1650	1912
66	336239.5.dec	3323385H1	1661	1910
66	336239.5.dec	1719741F6	1679	2142
66	336239.5.dec	1719741H1	1679	1911
66	336239.5.dec	2733751H1	1680	1939
66	336239.5.dec	2801762H1	1717	1981
66	336239.5.dec	2220513H1	1755	1988
66	336239.5.dec	608639H1	1832	2053
66	336239.5.dec	4356319H1	1833	2114
66	336239.5.dec	1923732R6	1840	2293
66	336239.5.dec	1923732H1	1840	2108
66	336239.5.dec	4210965H1	1860	2040
66	336239.5.dec	1785944H1	1862	2057
66	336239.5.dec	1267976F1	1899	2435
66	336239.5.dec	1267976H1	1899	2155
66	336239.5.dec	g2737159	1904	2292
66	336239.5.dec	5449665H1	1914	2164
66	336239.5.dec	6122507H1	1919	2495
66	336239.5.dec	6122807H1	1919	1985
66	336239.5.dec	3698691H1	1929	2191
66	336239.5.dec	2871258H1	1947	2224
66	336239.5.dec	g3004362	2007	2329
66	336239.5.dec	4584944H1	2021	2274

Table 4

66	336239.5.dec	3013346H1	2080	2354
66	336239.5.dec	3502187H1	2081	2367
66	336239.5.dec	2861426T6	2086	2556
66	336239.5.dec	995243H1	2097	2354
66	336239.5.dec	1821619F6	2098	2587
66	336239.5.dec	1821619H1	2098	2334
66	336239.5.dec	1923732T6	2115	2568
66	336239.5.dec	4650712H1	2116	2382
66	336239.5.dec	1719741T6	2129	2558
66	336239.5.dec	2651489H1	2130	2371
66	336239.5.dec	g1849169	2133	2578
66	336239.5.dec	g3367258	2147	2606
66	336239.5.dec	g4270156	2154	2606
66	336239.5.dec	g4486416	2159	2611
66	336239.5.dec	1821619T6	2168	2565
66	336239.5.dec	g5394396	2167	2611
66	336239.5.dec	4088855H1	2170	2443
66	336239.5.dec	g4373611	2172	2602
66	336239.5.dec	g5630634	2175	2555
66	336239.5.dec	2448329H1	2183	2437
66	336239.5.dec	2126858H1	2186	2451
66	336239.5.dec	g3052869	2189	2606
66	336239.5.dec	2597895F6	2200	2606
66	336239.5.dec	4896837H1	2200	2503
66	336239.5.dec	2597895H1	2200	2466
66	336239.5.dec	5986132H1	2201	2416
66	336239.5.dec	g4438961	2204	2595
66	336239.5.dec	g2537971	2213	2607
66	336239.5.dec	g4453236	2218	2555
66	336239.5.dec	g1860418	2229	2604
66	336239.5.dec	g3839639	2239	2555
66	336239.5.dec	g4762107	2245	2602
66	336239.5.dec	g4435892	2260	2604
66	336239.5.dec	g4900173	2274	2552
66	336239.5.dec	g4569426	2276	2555
66	336239.5.dec	g3190842	2294	2605
66	336239.5.dec	4022527H1	2373	2651
66	336239.5.dec	3945770H1	2374	2650
66	336239.5.dec	g2905130	2378	2602
66	336239.5.dec	g789334	2384	2567
66	336239.5.dec	g2584105	2473	2602
67	215660.4.dec	4728087H1	150	415
67	215660.4.dec	g1638041	158	389
67	215660.4.dec	3949305H1	38	322
67	215660.4.dec	g689887	38	468
67	215660.4.dec	3325969H1	236	479
67	215660.4.dec	3799417H1	238	524
67	215660.4.dec	g1557211	246	675
67	215660.4.dec	3676390H1	18	296
67	215660.4.dec	3797049H1	17	233
67	215660.4.dec	1857506H1	18	181
67	215660.4.dec	2498312H1	18	257
67	215660.4.dec	3255981H1	28	264
67	215660.4.dec	g1954009	35	393
67	215660.4.dec	3333763H1	37	322
67	215660.4.dec	1893878H1	37	274
67	215660.4.dec	946626H1	19	231
67	215660.4.dec	g1990338	20	389
67	215660.4.dec	804328H1	21	263
67	215660.4.dec	g1648082	20	258
67	215660.4.dec	5604792H1	715	962
67	215660.4.dec	4886452H1	728	958
67	215660.4.dec	5950537H1	610	856
67	215660.4.dec	3971078H1	616	885
67	215660.4.dec	g2007990	48	279
67	215660.4.dec	799172H1	66	300
67	215660.4.dec	2814381H1	638	874
67	215660.4.dec	g1147549	667	1066
67	215660.4.dec	g894725	673	993
67	215660.4.dec	g1938999	406	892
67	215660.4.dec	g2307107	410	845
67	215660.4.dec	2235577H1	428	669
67	215660.4.dec	4976668H1	683	948
67	215660.4.dec	1857506F6	18	356
67	215660.4.dec	986459H1	18	311
67	215660.4.dec	3674390H1	18	298
67	215660.4.dec	1894195H1	37	265
67	215660.4.dec	5347189H1	37	236
67	215660.4.dec	g1966826	314	749
67	215660.4.dec	g1968580	338	769
67	215660.4.dec	3722329H1	403	696
67	215660.4.dec	1917371H1	622	888
67	215660.4.dec	4205106H1	636	929
67	215660.4.dec	2523041H1	1	231
67	215660.4.dec	2559345H1	3	257
67	215660.4.dec	5426049H1	4	225
67	215660.4.dec	3136554H1	18	299
67	215660.4.dec	2540242H1	18	251
67	215660.4.dec	2612738H1	19	259
67	215660.4.dec	3900056H1	19	257
67	215660.4.dec	g1928635	529	953
67	215660.4.dec	4309267H1	543	852
67	215660.4.dec	g1406532	559	684
67	215660.4.dec	603142R1	597	1220
67	215660.4.dec	603142H1	597	842
67	215660.4.dec	5280718H1	599	801
67	215660.4.dec	g1194412	516	871
67	215660.4.dec	3045477H1	22	294
67	215660.4.dec	2528789H1	26	189
67	215660.4.dec	2532406H1	28	266
67	215660.4.dec	3053059H1	219	515
67	215660.4.dec	1363259H1	236	506
67	215660.4.dec	4112589H1	208	467
67	215660.4.dec	4923710H1	159	431
67	215660.4.dec	4308020H1	170	434
67	215660.4.dec	4307924H1	170	516
67	215660.4.dec	2417463H1	201	439
67	215660.4.dec	2416965H1	201	424
67	215660.4.dec	g727016	463	735
67	215660.4.dec	g2165443	463	824
67	215660.4.dec	4213686H1	465	649
67	215660.4.dec	1686857H1	466	671
67	215660.4.dec	4194806H1	467	778
67	215660.4.dec	5158759H1	445	666
67	215660.4.dec	3968785H1	616	882
67	215660.4.dec	g1312114	741	795
67	215660.4.dec	g3042998	1110	1505
67	215660.4.dec	4558627H1	748	1011
67	215660.4.dec	4558506H1	748	1009
67	215660.4.dec	1388105H1	751	989
67	215660.4.dec	3719731H1	800	943
67	215660.4.dec	g2163719	1115	1507
67	215660.4.dec	g1448573	825	1028
67	215660.4.dec	344302H1	827	1034
67	215660.4.dec	g1425193	837	1287
67	215660.4.dec	3021782H1	852	1130
67	215660.4.dec	5437401H1	857	1100
67	215660.4.dec	6536839H1	880	1399
67	215660.4.dec	1857506T6	902	1464
67	215660.4.dec	g2964295	1115	1505
67	215660.4.dec	g3888385	1119	1502
67	215660.4.dec	g4331608	1121	1504
67	215660.4.dec	g3431247	1123	1503
67	215660.4.dec	402462H1	934	1186

Table 4

67	215660.4.dec	g3230003	1124	1502
67	215660.4.dec	g1406428	1139	1503
67	215660.4.dec	g825910	1152	1511
67	215660.4.dec	2407832H1	953	1223
67	215660.4.dec	3453858H2	1146	1357
67	215660.4.dec	g4510545	1149	1510
67	215660.4.dec	3813776H1	1151	1446
67	215660.4.dec	g2778848	1153	1507
67	215660.4.dec	g2954358	1153	1503
67	215660.4.dec	g3146548	1156	1507
67	215660.4.dec	g3884641	1163	1507
67	215660.4.dec	3845459H1	962	1273
67	215660.4.dec	2679285H1	962	1237
67	215660.4.dec	g2208751	1166	1510
67	215660.4.dec	g3051605	1169	1503
67	215660.4.dec	1570357H1	962	1150
67	215660.4.dec	2132352T6	1174	1469
67	215660.4.dec	2132352H1	1179	1453
67	215660.4.dec	2132352R6	1179	1503
67	215660.4.dec	1570364H1	962	1146
67	215660.4.dec	g3250250	1202	1503
67	215660.4.dec	g1125205	1205	1501
67	215660.4.dec	g1928636	1205	1503
67	215660.4.dec	g1423883	1209	1492
67	215660.4.dec	g2278880	1212	1503
67	215660.4.dec	6521070H1	1224	1502
67	215660.4.dec	2426163H1	973	1200
67	215660.4.dec	g3154845	1229	1505
67	215660.4.dec	g4089301	1239	1509
67	215660.4.dec	g928688	979	1244
67	215660.4.dec	g1491527	990	1270
67	215660.4.dec	5907448H1	994	1312
67	215660.4.dec	523987H1	1019	1252
67	215660.4.dec	3603891H1	1025	1312
67	215660.4.dec	2274209H1	1026	1310
67	215660.4.dec	g2880850	1030	1503
67	215660.4.dec	2839076H1	1035	1290
67	215660.4.dec	g2824743	1036	1508
67	215660.4.dec	641418H1	1038	1294
67	215660.4.dec	g3015820	1043	1506
67	215660.4.dec	2561189H1	1047	1317
67	215660.4.dec	g1367968	1047	1485
67	215660.4.dec	118537H1	1049	1199
67	215660.4.dec	g4005382	1059	1511
67	215660.4.dec	g1367910	1074	1503
67	215660.4.dec	008834H1	1063	1364
67	215660.4.dec	g3401747	1079	1512
67	215660.4.dec	g2779406	1087	1504
67	215660.4.dec	g5112548	1089	1503
67	215660.4.dec	g5177242	1091	1512
67	215660.4.dec	2157703T6	1099	1465
67	215660.4.dec	g4077133	1108	1511
67	215660.4.dec	g2557366	1240	1501
67	215660.4.dec	g2839461	1242	1512
67	215660.4.dec	g1491453	1250	1503
67	215660.4.dec	g894679	1253	1491
67	215660.4.dec	g726966	1258	1498
67	215660.4.dec	g2969821	1276	1504
67	215660.4.dec	g3150603	1279	1503
67	215660.4.dec	g2736776	1292	1385
67	215660.4.dec	g1271203	1336	1515
67	215660.4.dec	g3778319	1355	1502
67	215660.4.dec	608744H1	1359	1503
67	215660.4.dec	g4525841	1370	1508
67	215660.4.dec	1980051H1	1373	1502
67	215660.4.dec	g2704354	1403	1505
67	215660.4.dec	g1189214	1418	1512
67	215660.4.dec	4797457H1	15	240
67	215660.4.dec	3324029H1	13	319
67	215660.4.dec	5668158H1	12	243
67	215660.4.dec	2666214H1	15	273
67	215660.4.dec	4919274H1	17	275
67	215660.4.dec	1632851H1	17	429
67	215660.4.dec	2128217H1	517	778
68	391940.2.dec	g1557429	2656	2737
68	391940.2.dec	2085379H1	2676	2769
68	391940.2.dec	g1693291	2675	3128
68	391940.2.dec	g3167046	2680	3127
68	391940.2.dec	g751398	2763	2859
68	391940.2.dec	2702823H1	2693	2863
68	391940.2.dec	1000364H1	2696	2769
68	391940.2.dec	g1425705	2698	2830
68	391940.2.dec	5741371H1	2702	2769
68	391940.2.dec	1689136F6	2712	3243
68	391940.2.dec	1689136H1	2712	2769
68	391940.2.dec	1476678H1	2543	2742
68	391940.2.dec	909385H1	2587	2769
68	391940.2.dec	217954H1	2589	2811
68	391940.2.dec	214949H1	2589	2767
68	391940.2.dec	3813492H1	2604	2831
68	391940.2.dec	g2988090	2610	2769
68	391940.2.dec	2847338H1	2621	2769
68	391940.2.dec	2568270H1	2621	2769
68	391940.2.dec	652869H1	2633	2787
68	391940.2.dec	g4393629	2671	2769
68	391940.2.dec	4333183H1	2645	2780
68	391940.2.dec	g698302	2646	3005
68	391940.2.dec	5710267H2	2656	2792
68	391940.2.dec	5404183H1	2014	2235
68	391940.2.dec	4138469H1	2130	2423
68	391940.2.dec	2817316H1	2135	2447
68	391940.2.dec	2817316F6	2135	2639
68	391940.2.dec	3692035H1	2140	2414
68	391940.2.dec	1329527H1	2203	2337
68	391940.2.dec	2633655H1	2215	2471
68	391940.2.dec	2612237H1	2217	2431
68	391940.2.dec	2507857H1	2225	2484
68	391940.2.dec	3498770H1	2228	2427
68	391940.2.dec	5309067H1	2229	2424
68	391940.2.dec	5309085H1	2229	2387
68	391940.2.dec	3591236H1	2249	2556
68	391940.2.dec	668908H1	2257	2542
68	391940.2.dec	3617329H1	2278	2513
68	391940.2.dec	g2464153	2289	2683
68	391940.2.dec	g1275547	2309	2511
68	391940.2.dec	3595319H1	2313	2643
68	391940.2.dec	g1242878	2324	2685
68	391940.2.dec	g2241102	2337	2744
68	391940.2.dec	3813492F6	2358	2831
68	391940.2.dec	526033H1	2448	2704
68	391940.2.dec	2846889H1	2447	2705
68	391940.2.dec	526010H1	2449	2688
68	391940.2.dec	1975137H1	2450	2690
68	391940.2.dec	g982969	2529	2625
68	391940.2.dec	g3070059	2714	2952
68	391940.2.dec	g4738191	2713	2952
68	391940.2.dec	g4648157	2713	2769
68	391940.2.dec	g4682847	2713	2952
68	391940.2.dec	g1224334	2714	3154
68	391940.2.dec	5157173H2	1	110
68	391940.2.dec	4648337F6	1	552
68	391940.2.dec	4648337H1	2	223
68	391940.2.dec	3153717H1	79	312
68	391940.2.dec	6263536H1	160	627

Table 4

68	391940.2.dec	5322043H1	158	420
68	391940.2.dec	g317583	297	578
68	391940.2.dec	4782861T6	327	859
68	391940.2.dec	4648337T6	328	866
68	391940.2.dec	4731271T6	348	864
68	391940.2.dec	789364R6	350	665
68	391940.2.dec	199073H1	3203	3255
68	391940.2.dec	g3959096	3222	3303
68	391940.2.dec	2546814H1	3237	3326
68	391940.2.dec	1612728H1	3248	3326
68	391940.2.dec	6432229H1	3034	3326
68	391940.2.dec	g1061926	3042	3256
68	391940.2.dec	6427691H1	3050	3326
68	391940.2.dec	2667645H1	3050	3281
68	391940.2.dec	2824232H1	3053	3349
68	391940.2.dec	g2988010	3055	3261
68	391940.2.dec	g2984791	3062	3256
68	391940.2.dec	g647798	3064	3330
68	391940.2.dec	966393H1	3117	3326
68	391940.2.dec	3010912H1	3121	3323
68	391940.2.dec	g2358957	3137	3326
68	391940.2.dec	3874648H1	3147	3347
68	391940.2.dec	g1061927	2713	2898
68	391940.2.dec	209520H1	2748	2896
68	391940.2.dec	4422068H1	2768	2916
68	391940.2.dec	788564T6	2810	3212
68	391940.2.dec	g3889856	2819	3256
68	391940.2.dec	g1243333	2876	3250
68	391940.2.dec	g2002565	2883	3250
68	391940.2.dec	g969305	2893	3041
68	391940.2.dec	g823322	2909	3263
68	391940.2.dec	g4535621	2953	3250
68	391940.2.dec	2077084T6	2984	3213
68	391940.2.dec	g1694279	2989	3255
68	391940.2.dec	3519539H1	2998	3198
68	391940.2.dec	6436535H1	3005	3255
68	391940.2.dec	g799773	3009	3255
68	391940.2.dec	3101145H1	3010	3297
68	391940.2.dec	g4901206	3028	3254
68	391940.2.dec	2069671T6	3029	3218
68	391940.2.dec	2534382H2	3029	3200
68	391940.2.dec	g4629916	3029	3255
68	391940.2.dec	3650567H1	3029	3246
68	391940.2.dec	g678131	3029	3255
68	391940.2.dec	2817316T6	3029	3217
68	391940.2.dec	g4850987	3030	3255
68	391940.2.dec	g1693240	3030	3255
68	391940.2.dec	g2241050	3030	3255
68	391940.2.dec	g2553045	3030	3253
68	391940.2.dec	6324661H1	3030	3144
68	391940.2.dec	3841263H1	3030	3170
68	391940.2.dec	2687078H1	3159	3305
68	391940.2.dec	4080534H1	3164	3326
68	391940.2.dec	6569059H1	3030	3255
68	391940.2.dec	336881F1	3166	3255
68	391940.2.dec	336896H1	3165	3250
68	391940.2.dec	g4084228	3030	3255
68	391940.2.dec	928254H1	3176	3326
68	391940.2.dec	6350218H2	3030	3119
68	391940.2.dec	3120274F6	3178	3326
68	391940.2.dec	g1694387	3030	3194
68	391940.2.dec	g5636347	3030	3255
68	391940.2.dec	g1965608	3030	3255
68	391940.2.dec	3120258H1	3178	3305
68	391940.2.dec	5495516H1	3189	3326
68	391940.2.dec	3798874H1	3030	3111
68	391940.2.dec	148197H1	3194	3305
68	391940.2.dec	789364R1	350	884
68	391940.2.dec	789364H1	350	566
68	391940.2.dec	3596716H1	377	586
68	391940.2.dec	114511H1	400	579
68	391940.2.dec	569933H1	446	511
68	391940.2.dec	5605517H1	510	681
68	391940.2.dec	g1858975	549	953
68	391940.2.dec	6431523H1	680	1142
68	391940.2.dec	4020548H1	741	845
68	391940.2.dec	2489839H1	738	991
68	391940.2.dec	3128649H1	802	868
68	391940.2.dec	3341237H1	806	1053
68	391940.2.dec	6351274H2	807	1158
68	391940.2.dec	6505585H1	843	1332
68	391940.2.dec	5004941H1	886	1143
68	391940.2.dec	4099113H1	961	1262
68	391940.2.dec	3205913H1	968	1247
68	391940.2.dec	g774270	979	1347
68	391940.2.dec	2069671H1	1066	1322
68	391940.2.dec	2069671F6	1066	1377
68	391940.2.dec	3939276H1	1084	1247
68	391940.2.dec	2633121H1	1193	1436
68	391940.2.dec	2631615H1	1193	1464
68	391940.2.dec	5312304H1	1250	1415
68	391940.2.dec	g775835	1253	1567
68	391940.2.dec	3433173H1	1294	1532
68	391940.2.dec	3036880H1	1328	1598
68	391940.2.dec	5091289H1	1362	1633
68	391940.2.dec	g705608	1379	1697
68	391940.2.dec	g5452920	1391	1856
68	391940.2.dec	2077084F6	1395	1813
68	391940.2.dec	2077084H1	1395	1662
68	391940.2.dec	g1858926	1445	1833
68	391940.2.dec	3473107H1	1463	1711
68	391940.2.dec	2170438H1	1536	1771
68	391940.2.dec	3978711H1	1549	1831
68	391940.2.dec	3602690H1	1618	1908
68	391940.2.dec	5263190H1	1663	1894
68	391940.2.dec	788564H1	1689	1904
68	391940.2.dec	g983004	1758	2113
68	391940.2.dec	6106301H1	1782	2108
68	391940.2.dec	3573367H1	1790	2084
68	391940.2.dec	g983003	1796	1972
68	391940.2.dec	2494274H1	1797	2100
68	391940.2.dec	3357432H1	1832	2088
68	391940.2.dec	366335R6	1872	2226
68	391940.2.dec	366335H1	1872	2108
68	391940.2.dec	4674184H1	1875	2139
68	391940.2.dec	2273833H1	1875	2122
68	391940.2.dec	2686781H1	1887	2076
68	391940.2.dec	2687319H1	1887	2139
68	391940.2.dec	g769399	1891	2174
68	391940.2.dec	657187H1	1911	2172
68	391940.2.dec	4819935H1	1916	2197
68	391940.2.dec	3952060H1	1920	2189
68	391940.2.dec	5742076H1	1951	2216
68	391940.2.dec	1318431H1	1981	2223
68	391940.2.dec	2432247H1	1989	2203
69	978302.3.dec	3070474H1	55	311
69	978302.3.dec	3580385H1	52	314
69	978302.3.dec	3456668H1	55	234
69	978302.3.dec	g4530434	64	2553
69	978302.3.dec	2893122H1	62	321
69	978302.3.dec	g1966219	66	416
69	978302.3.dec	3089177H1	84	356
69	978302.3.dec	3673761H1	88	245
69	978302.3.dec	5542071H1	98	306

Table 4

69	978302.3.dec	4049703H1	97	382
69	978302.3.dec	3273789H1	110	357
69	978302.3.dec	4803070H1	311	568
69	978302.3.dec	5502955R6	345	751
69	978302.3.dec	g3330490	449	844
69	978302.3.dec	g916384	496	716
69	978302.3.dec	4570560H1	508	772
69	978302.3.dec	4799067H1	536	814
69	978302.3.dec	5990884H1	554	849
69	978302.3.dec	6421386H1	684	1179
69	978302.3.dec	449422H1	709	952
69	978302.3.dec	1303054H1	746	977
69	978302.3.dec	3494973H1	826	1129
69	978302.3.dec	2762433H1	883	1137
69	978302.3.dec	671218H1	883	1139
69	978302.3.dec	5374645H1	943	1204
69	978302.3.dec	4293786H1	962	1115
69	978302.3.dec	g30733	1008	1310
69	978302.3.dec	1556785H1	1045	1237
69	978302.3.dec	1557004H1	1045	1247
69	978302.3.dec	1554631H1	1045	1214
69	978302.3.dec	g4220895	1067	2218
69	978302.3.dec	2667190H1	1096	1343
69	978302.3.dec	3389771H1	1115	1406
69	978302.3.dec	g1296252	1145	1477
69	978302.3.dec	495467H1	1144	1392
69	978302.3.dec	495467R6	1144	1621
69	978302.3.dec	469485R1	1184	1693
69	978302.3.dec	469485H1	1184	1418
69	978302.3.dec	g2783215	1290	1698
69	978302.3.dec	5117988H1	1427	1697
69	978302.3.dec	2656968H1	1447	1679
69	978302.3.dec	044893H1	1457	1621
69	978302.3.dec	g2023688	1493	1815
69	978302.3.dec	2649157H1	1493	1722
69	978302.3.dec	5392455H1	1535	1805
69	978302.3.dec	2972663H2	1540	1812
69	978302.3.dec	4887906H1	1548	1784
69	978302.3.dec	1494628H1	1565	1777
69	978302.3.dec	4123045H2	1577	1833
69	978302.3.dec	598817H1	1592	1744
69	978302.3.dec	g1697464	1592	1873
69	978302.3.dec	2782445H1	1595	1839
69	978302.3.dec	3071188H1	1599	1864
69	978302.3.dec	1499678F6	1611	1983
69	978302.3.dec	1499678H1	1611	1833
69	978302.3.dec	3605819H1	1627	1786
69	978302.3.dec	2603477H1	1645	1890
69	978302.3.dec	5396451H1	1714	1966
69	978302.3.dec	g1925214	1718	2183
69	978302.3.dec	6410645H1	1726	2080
69	978302.3.dec	g1923462	1725	2117
69	978302.3.dec	5563939H1	1739	1949
69	978302.3.dec	3901151H1	1746	2017
69	978302.3.dec	3467260H1	1765	1865
69	978302.3.dec	2153778H1	1772	1913
69	978302.3.dec	2363625F6	1792	2120
69	978302.3.dec	2363625H1	1792	2020
69	978302.3.dec	6167007H1	1803	2363
69	978302.3.dec	2363625T6	1814	2354
69	978302.3.dec	043817H1	1819	2062
69	978302.3.dec	1627118H1	1835	1935
69	978302.3.dec	1627118F6	1835	2274
69	978302.3.dec	904267H1	1840	2062
69	978302.3.dec	4921037H1	1	290
69	978302.3.dec	4913159H1	31	294
69	978302.3.dec	g4838128	44	2568
69	978302.3.dec	5504612H1	41	112
69	978302.3.dec	1903639H1	42	296
69	978302.3.dec	3580385F6	52	446
69	978302.3.dec	5537637H1	51	229
69	978302.3.dec	904267R2	1840	2291
69	978302.3.dec	004607H1	1842	2021
69	978302.3.dec	g2141685	1866	2354
69	978302.3.dec	g2111916	1877	2317
69	978302.3.dec	5314445H1	1895	2139
69	978302.3.dec	575430T6	1938	2513
69	978302.3.dec	2962839H1	1947	2232
69	978302.3.dec	3580385T6	1949	2513
69	978302.3.dec	469485F1	1956	2552
69	978302.3.dec	629855H1	1972	2105
69	978302.3.dec	6590117H1	1976	2552
69	978302.3.dec	6590017H1	1976	2505
69	978302.3.dec	4508845H1	2014	2296
69	978302.3.dec	2878353H1	2019	2175
69	978302.3.dec	2573374H1	2027	2280
69	978302.3.dec	2573245H1	2027	2266
69	978302.3.dec	412698H1	2043	2251
69	978302.3.dec	g4302126	2084	2552
69	978302.3.dec	g3884354	2097	2554
69	978302.3.dec	g3434749	2099	2552
69	978302.3.dec	g5100695	2104	2551
69	978302.3.dec	4914418H1	2117	2363
69	978302.3.dec	816019R1	2128	2548
69	978302.3.dec	816019R6	2128	2481
69	978302.3.dec	816019H1	2128	2363
69	978302.3.dec	g2727063	2138	2488
69	978302.3.dec	g5631519	2140	2552
69	978302.3.dec	g4268066	2143	2552
69	978302.3.dec	g3038701	2146	2554
69	978302.3.dec	g2905509	2168	2552
69	978302.3.dec	g2337320	2170	2553
69	978302.3.dec	g5392280	2174	2554
69	978302.3.dec	g2433438	2176	2551
69	978302.3.dec	g4764364	2181	2551
69	978302.3.dec	g4900354	2181	2560
69	978302.3.dec	3455054H1	2195	2459
69	978302.3.dec	3406692H1	2206	2456
69	978302.3.dec	g2767388	2211	2558
69	978302.3.dec	g3960728	2213	2552
69	978302.3.dec	1627118T6	2212	2512
69	978302.3.dec	g2751958	2213	2543
69	978302.3.dec	g2969710	2220	2555
69	978302.3.dec	g2839836	2219	2552
69	978302.3.dec	1499678T6	2223	2506
69	978302.3.dec	2244852T6	2227	2510
69	978302.3.dec	g2849258	2234	2552
69	978302.3.dec	2780422H1	2241	2476
69	978302.3.dec	5037261H1	2250	2433
69	978302.3.dec	g1924159	2256	2552
69	978302.3.dec	g5657243	2257	2552
69	978302.3.dec	g2111854	2259	2559
69	978302.3.dec	g1925215	2269	2563
69	978302.3.dec	g824152	2307	2563
69	978302.3.dec	2511077H1	2321	2549
69	978302.3.dec	g1265044	2322	2552
69	978302.3.dec	627673H1	2324	2549
69	978302.3.dec	g3118123	2331	2552
69	978302.3.dec	927354R1	2346	2599
69	978302.3.dec	927354H1	2348	2593
69	978302.3.dec	3241557T6	2366	2510
69	978302.3.dec	790882R1	2367	2552
69	978302.3.dec	790882F1	2367	2552
69	978302.3.dec	039176H1	2375	2542

Table 4

69	978302.3.dec	g1218452	2418	2554
69	978302.3.dec	1649824H1	2444	2585
69	978302.3.dec	g1957671	2454	2599
69	978302.3.dec	g3960735	2464	2552
69	978302.3.dec	4274132H1	2471	2609
70	228629.11.dec	g2934289	1704	2059
70	228629.11.dec	g2102954	1705	2089
70	228629.11.dec	g3147325	1707	2091
70	228629.11.dec	001420H1	1699	2104
70	228629.11.dec	1294966H1	1119	1358
70	228629.11.dec	6374472H1	1119	1359
70	228629.11.dec	2743486H1	1193	1430
70	228629.11.dec	4531151H1	1122	1400
70	228629.11.dec	6359587H2	1197	1749
70	228629.11.dec	5734367H1	1175	1374
70	228629.11.dec	892335H1	1758	1948
70	228629.11.dec	g648436	1762	2100
70	228629.11.dec	975009H1	1776	2069
70	228629.11.dec	g3889950	1810	2086
70	228629.11.dec	887059H1	1839	2085
70	228629.11.dec	869989H1	1840	2086
70	228629.11.dec	869854H1	1840	2085
70	228629.11.dec	g1626689	1735	2084
70	228629.11.dec	g3921132	1743	2093
70	228629.11.dec	856889H1	1754	1937
70	228629.11.dec	3614651H1	1	217
70	228629.11.dec	2689769H1	17	269
70	228629.11.dec	2689769F6	17	478
70	228629.11.dec	6112670H1	27	280
70	228629.11.dec	g603230	50	2085
70	228629.11.dec	6534961H1	63	490
70	228629.11.dec	410074H1	129	368
70	228629.11.dec	3717155H1	246	474
70	228629.11.dec	5301716H1	322	592
70	228629.11.dec	6290096H1	577	811
70	228629.11.dec	2911910H1	590	856
70	228629.11.dec	1300552H1	607	836
70	228629.11.dec	1413704H1	625	902
70	228629.11.dec	3661737H1	659	934
70	228629.11.dec	4434566H1	735	990
70	228629.11.dec	1976292H1	796	1038
70	228629.11.dec	6297547H1	804	1068
70	228629.11.dec	910262H1	827	1122
70	228629.11.dec	1701222H1	827	1038
70	228629.11.dec	6131544H1	850	1153
70	228629.11.dec	6361603H2	891	1430
70	228629.11.dec	1433660H1	898	1136
70	228629.11.dec	1395790H1	951	1201
70	228629.11.dec	3253094H1	959	1157
70	228629.11.dec	4710208H1	974	1235
70	228629.11.dec	6490580H1	1001	1377
70	228629.11.dec	6490280H1	1001	1460
70	228629.11.dec	4749725H1	1006	1274
70	228629.11.dec	1651252H1	1006	1249
70	228629.11.dec	1974061H1	1031	1295
70	228629.11.dec	2412754H1	1033	1259
70	228629.11.dec	4438041H1	1052	1290
70	228629.11.dec	4437941H1	1052	1293
70	228629.11.dec	g715781	1114	1395
70	228629.11.dec	g2141297	1480	1638
70	228629.11.dec	3228693T6	1484	2060
70	228629.11.dec	207391H1	1929	2085
70	228629.11.dec	211562H1	1929	2085
70	228629.11.dec	3566051H1	1415	1651
70	228629.11.dec	388535H1	1421	1701
70	228629.11.dec	505367H1	1432	1643
70	228629.11.dec	1358153H1	1434	1682
70	228629.11.dec	312757H1	1437	1655
70	228629.11.dec	312451H1	1438	1604
70	228629.11.dec	312476H1	1438	1604
70	228629.11.dec	2639058H1	1437	1688
70	228629.11.dec	2328889H1	1523	1816
70	228629.11.dec	2751426H1	1457	1716
70	228629.11.dec	4344049H1	1462	1753
70	228629.11.dec	3771512H1	1462	1733
70	228629.11.dec	2099424H1	1473	1739
70	228629.11.dec	025702H1	1231	1388
70	228629.11.dec	882702H1	1372	1626
70	228629.11.dec	g5365368	1864	2085
70	228629.11.dec	3088319H1	1868	2085
70	228629.11.dec	g2782978	1882	2085
70	228629.11.dec	3932184H1	1452	1729
70	228629.11.dec	6587364H1	1378	1921
70	228629.11.dec	1296630H1	1380	1596
70	228629.11.dec	3126240H1	1380	1655
70	228629.11.dec	1979479H1	1383	1654
70	228629.11.dec	2585217H1	1324	1571
70	228629.11.dec	g756027	1283	1509
70	228629.11.dec	955073H1	1361	1648
70	228629.11.dec	2528386H1	1536	1858
70	228629.11.dec	1225607H1	1548	1788
70	228629.11.dec	301236H1	1439	1648
70	228629.11.dec	231848H1	1438	1610
70	228629.11.dec	5185095H1	1444	1675
70	228629.11.dec	3502894H1	1447	1731
70	228629.11.dec	1800594H1	1518	1729
70	228629.11.dec	g1331191	1522	1956
70	228629.11.dec	1800568H1	1518	1740
70	228629.11.dec	476384H1	1654	1922
70	228629.11.dec	1752755H1	1661	1913
70	228629.11.dec	1754354H1	1661	1907
70	228629.11.dec	g834745	1663	1935
70	228629.11.dec	g838552	1663	1890
70	228629.11.dec	g4686244	1673	2085
70	228629.11.dec	4730903H1	1612	1880
70	228629.11.dec	g4188496	1639	2090
70	228629.11.dec	4633239H1	1640	1885
70	228629.11.dec	004785H1	1581	1877
70	228629.11.dec	4596660H1	1583	1841
70	228629.11.dec	5951768H1	1588	1934
70	228629.11.dec	5321992H1	1598	1863
70	228629.11.dec	5004692H1	1598	1839
70	228629.11.dec	6103423H1	1549	1851
70	228629.11.dec	221523H1	1550	1656
70	228629.11.dec	3450038H1	1555	1798
70	228629.11.dec	541569H1	1575	1796
70	228629.11.dec	816658H1	1575	1812
70	228629.11.dec	2104606H1	1385	1645
70	228629.11.dec	5927924H1	1387	1682
70	228629.11.dec	1496306H1	1409	1650
70	228629.11.dec	2770041H1	1690	1943
70	228629.11.dec	1751734H1	1698	1922
70	228629.11.dec	3164903H1	1698	1985
71	011211.5.dec	g3229245	1492	1675
71	011211.5.dec	g3055421	1589	1677
71	011211.5.dec	g2355252	1517	1668
71	011211.5.dec	g4307448	1534	1669
71	011211.5.dec	4422963H1	252	499
71	011211.5.dec	4422989H1	252	485
71	011211.5.dec	3899914H1	266	534
71	011211.5.dec	1796354H1	291	508
71	011211.5.dec	g1329775	351	625
71	011211.5.dec	3248726H1	374	682
71	011211.5.dec	4583315H1	395	674

Table 4

71	011211.5.dec	730632H1	414	637	71	011211.5.dec	g2785911	1312	1665
71	011211.5.dec	790391R1	429	1010	71	011211.5.dec	2500452F6	1	490
71	011211.5.dec	790391H1	429	671	71	011211.5.dec	2500452H1	1	267
71	011211.5.dec	4518427H1	442	687	71	011211.5.dec	2504526H1	50	289
71	011211.5.dec	2935816H1	445	695	71	011211.5.dec	2485204H1	130	370
71	011211.5.dec	2722677F6	470	965	71	011211.5.dec	4590655H1	205	450
71	011211.5.dec	1788251H1	563	812	71	011211.5.dec	1686319H1	205	396
71	011211.5.dec	5116027H1	567	827	71	011211.5.dec	3211206H1	205	327
71	011211.5.dec	5116074H1	567	821	71	011211.5.dec	3411833H1	205	437
71	011211.5.dec	3986358H1	596	792	71	011211.5.dec	3271955H1	205	464
71	011211.5.dec	4203841H1	612	909	71	011211.5.dec	g2161312	1211	1669
71	011211.5.dec	5314859H1	675	815	71	011211.5.dec	g1358211	1227	1675
71	011211.5.dec	3740285H1	1313	1599	71	011211.5.dec	g1801782	1241	1670
71	011211.5.dec	5121062T6	1314	1660	71	011211.5.dec	g4153547	1241	1669
71	011211.5.dec	g4664357	1318	1671	71	011211.5.dec	g1317339	1255	1669
71	011211.5.dec	g1940230	1324	1650	71	011211.5.dec	2395410T6	1256	1632
71	011211.5.dec	g2184545	1324	1650	71	011211.5.dec	1811608T6	1262	1629
71	011211.5.dec	g3665509	1326	1676	71	011211.5.dec	3488381T6	1262	1627
71	011211.5.dec	2722677T6	1338	1627	71	011211.5.dec	g5674690	1262	1671
71	011211.5.dec	g2952637	1338	1673	71	011211.5.dec	536468H1	1269	1522
71	011211.5.dec	2474881H1	173	407	71	011211.5.dec	730632F1	1185	1671
71	011211.5.dec	3580753H1	177	489	71	011211.5.dec	g5637214	1207	1671
71	011211.5.dec	3581452H1	177	467	71	011211.5.dec	1639808H1	1208	1418
71	011211.5.dec	486671H1	187	473	71	011211.5.dec	g5659631	1208	1668
71	011211.5.dec	2544119H1	194	447	71	011211.5.dec	2750833H1	1052	1190
71	011211.5.dec	6370602H1	204	312	71	011211.5.dec	2750833R6	1052	1313
71	011211.5.dec	5898419H1	204	489	71	011211.5.dec	6176275H1	1064	1344
71	011211.5.dec	3438381H1	204	455	71	011211.5.dec	628273H1	1064	1288
71	011211.5.dec	5121062F6	205	670	71	011211.5.dec	2525968H1	1067	1304
71	011211.5.dec	3784294H1	205	502	71	011211.5.dec	5954055H1	1090	1214
71	011211.5.dec	2107539H1	207	458	71	011211.5.dec	1534852T6	1102	1626
71	011211.5.dec	3732863H1	205	469	71	011211.5.dec	2354626H1	1110	1325
71	011211.5.dec	1721414H1	207	420	71	011211.5.dec	6603759H1	1125	1673
71	011211.5.dec	g1357922	205	599	71	011211.5.dec	6603659H1	1126	1583
71	011211.5.dec	2211136H1	208	407	71	011211.5.dec	5206520T6	1140	1643
71	011211.5.dec	2722677H1	470	713	71	011211.5.dec	780467T6	1157	1624
71	011211.5.dec	1811608F6	478	915	71	011211.5.dec	4837615H1	1160	1458
71	011211.5.dec	1811608H1	478	721	71	011211.5.dec	538428H1	1164	1311
71	011211.5.dec	1809182H1	504	669	71	011211.5.dec	6393337H1	813	1108
71	011211.5.dec	1979530H1	510	755	71	011211.5.dec	3438482H1	851	1098
71	011211.5.dec	6557538H1	516	1108	71	011211.5.dec	4185657H1	871	1086
71	011211.5.dec	5119348H1	522	817	71	011211.5.dec	6428245H1	891	1480
71	011211.5.dec	5313378H1	241	379	71	011211.5.dec	g2188554	894	1044
71	011211.5.dec	3342386H1	243	497	71	011211.5.dec	1212647H1	920	1152
71	011211.5.dec	4896741H1	252	543	71	011211.5.dec	2772091F6	929	1255
71	011211.5.dec	1514966H1	229	402	71	011211.5.dec	2772091H1	929	1176
71	011211.5.dec	3982780H1	234	509	71	011211.5.dec	3179605H1	945	1247
71	011211.5.dec	4731415H1	239	512	71	011211.5.dec	5816063H1	946	1181
71	011211.5.dec	g2659808	1475	1671	71	011211.5.dec	4691156H1	954	1182
71	011211.5.dec	g4307315	1488	1669	71	011211.5.dec	3411470H1	956	1210
71	011211.5.dec	2562177H1	205	462	71	011211.5.dec	4278241H1	970	1200
71	011211.5.dec	1865272H1	205	449	71	011211.5.dec	2920077H1	1021	1284
71	011211.5.dec	1865272F6	205	602	71	011211.5.dec	5119720H1	1027	1297
71	011211.5.dec	3053770H1	220	511	71	011211.5.dec	4939387H1	1037	1282
71	011211.5.dec	3057158H1	220	425	71	011211.5.dec	2750833T6	1041	1626
71	011211.5.dec	g1315022	224	665	71	011211.5.dec	2500452T6	1045	1623
71	011211.5.dec	2395410F6	224	572	71	011211.5.dec	1904368H1	1047	1338
71	011211.5.dec	2395410H1	224	463	71	011211.5.dec	1904368F6	1047	1344
71	011211.5.dec	5374094H1	224	437	71	011211.5.dec	g5540370	1392	1672
71	011211.5.dec	g1802011	227	661	71	011211.5.dec	1865272T6	1398	1839
71	011211.5.dec	g831726	229	623	71	011211.5.dec	2772091T6	1403	1625
71	011211.5.dec	g5636952	1271	1671	71	011211.5.dec	2158516H1	1427	1547
71	011211.5.dec	g5530755	1282	1673	71	011211.5.dec	g2321614	1427	1669
71	011211.5.dec	g5659613	1283	1668	71	011211.5.dec	g4565430	1434	1669
71	011211.5.dec	2589181H1	1304	1531	71	011211.5.dec	790391F1	1443	1669
71	011211.5.dec	g3214484	1309	1674	71	011211.5.dec	g2021003	1472	1659
71	011211.5.dec	g2354244	1310	1668	71	011211.5.dec	4129420H1	209	384

Table 4

71	011211.5.dec	4931939H1	213	502
71	011211.5.dec	5299520H1	212	447
71	011211.5.dec	778131H1	213	424
71	011211.5.dec	2995677H1	212	463
71	011211.5.dec	3528587H1	213	504
71	011211.5.dec	4192842H1	213	507
71	011211.5.dec	2828929H1	214	474
71	011211.5.dec	4689695H1	218	443
71	011211.5.dec	5299661H1	219	392
71	011211.5.dec	3783536H1	219	526
71	011211.5.dec	2432292H1	219	438
71	011211.5.dec	2230623H1	679	906
71	011211.5.dec	5578645H1	734	999
71	011211.5.dec	4884278H1	752	1013
71	011211.5.dec	3489306H1	756	1044
71	011211.5.dec	4859162H1	760	1036
71	011211.5.dec	3451104H1	765	1019
71	011211.5.dec	2605496H1	766	1012
71	011211.5.dec	4199159H1	782	1056
71	011211.5.dec	4858453H1	783	962
71	011211.5.dec	g5634460	792	878
71	011211.5.dec	1605934H1	809	1037
71	011211.5.dec	5106375H1	811	1052
71	011211.5.dec	1904368T6	1371	1629
71	011211.5.dec	g2875270	1371	1595
71	011211.5.dec	g2540410	1373	1672
71	011211.5.dec	g831607	1356	1680
71	011211.5.dec	6394443H1	1348	1612
71	011211.5.dec	g2184320	1375	1667

TABLE 5

SEQ ID NO:	Template ID	Tissue Distribution
1	405310.1.oct	Cardiovascular System - 16%, Germ Cells - 12%
2	480731.6.oct	Liver - 25%, Connective Tissue - 17%, Male Genitalia - 15%
3	334751.2.dec	Germ Cells - 33%, Liver - 24%, Endocrine System - 13%
4	237330.8.dec	Respiratory System - 60%, Male Genitalia - 40%
5	053778.11.dec	Embryonic Structures - 67%, Nervous System - 17%, Digestive System - 17%
6	360645.10.dec	Embryonic Structures - 67%, Nervous System - 11%
8	997089.7.dec	Sense Organs - 11%
9	237152.1.dec	Unclassified/Mixed - 41%, Germ Cells - 19%, Embryonic Structures - 13%, Respiratory System - 13%
10	232851.7.dec	Hemic and Immune System - 100%
11	083804.1.dec	Germ Cells - 70%, Connective Tissue - 16%
12	272721.6.oct	Digestive System - 10%
13	461603.4.oct	Germ Cells - 17%, Sense Organs - 14%, Musculoskeletal System - 10%
14	332465.2.dec	Connective Tissue - 100%
15	445175.3.dec	Germ Cells - 58%, Embryonic Structures - 20%, Male Genitalia - 17%
16	980541.1.dec	Nervous System - 50%, Embryonic Structures - 43%
17	237996.1.dec	Cardiovascular System - 21%, Exocrine Glands - 21%, Respiratory System - 16%, Digestive System - 16%, Hemic and Immune System - 16%
19	242082.10.dec	Female Genitalia - 75%, Hemic and Immune System - 25%
20	019239.1.dec	Exocrine Glands - 26%, Endocrine System - 17%, Hemic and Immune System - 17%
21	899943.1.dec	Sense Organs - 14%, Musculoskeletal System - 12%
22	443551.1.dec	Unclassified/Mixed - 50%, Nervous System - 27%, Female Genitalia - 14%
23	897957.1.dec	Pancreas - 44%, Liver - 27%, Male Genitalia - 10%
24	900911.1.dec	Germ Cells - 69%, Nervous System - 12%
25	999296.1.dec	Exocrine Glands - 22%, Endocrine System - 16%, Female Genitalia - 16%
26	442286.1.dec	Respiratory System - 50%, Exocrine Glands - 33%, Hemic and Immune System - 17%
27	901978.1.dec	Musculoskeletal System - 25%, Unclassified/Mixed - 18%, Hemic and Immune System - 13%
28	479346.1.dec	Unclassified/Mixed - 27%, Embryonic Structures - 20%, Skin - 14%
29	481750.1.dec	Male Genitalia - 29%, Urinary Tract - 13%, Skin - 11%
30	900917.2.dec	Respiratory System - 100%
31	999415.1.dec	Connective Tissue - 32%, Cardiovascular System - 32%, Exocrine Glands - 16%
32	900680.2.dec	Embryonic Structures - 34%, Liver - 19%, Unclassified/Mixed - 16%
33	902791.3.dec	Urinary Tract - 72%, Nervous System - 17%, Hemic and Immune System - 11%
34	053826.1.dec	Germ Cells - 69%, Unclassified/Mixed - 22%
35	204932.4.dec	NO DATA
36	400607.19.dec	Musculoskeletal System - 50%, Cardiovascular System - 29%, Nervous System - 21%
37	444248.7.dec	Exocrine Glands - 57%, Digestive System - 43%
38	346599.9.dec	Liver - 30%, Pancreas - 26%, Respiratory System - 21%
40	411396.24.dec	Male Genitalia - 100%
41	302819.4.dec	Exocrine Glands - 100%

TABLE 5

SEQ ID NO:	Template ID	Tissue Distribution
42	238734.2.dec	Skin - 94%
43	399525.3.dec	Unclassified/Mixed - 34%, Connective Tissue - 25%, Exocrine Glands - 13%
44	222795.6.dec	widely distributed
45	410628.5.dec	Sense Organs - 32%, Nervous System - 12%, Urinary Tract - 11%, Connective Tissue - 11%
46	053649.6.dec	Skin - 89%, Male Genitalia - 11%
47	221914.2.dec	Connective Tissue - 18%, Skin - 18%, Exocrine Glands - 13%
49	401482.2.oct	Skin - 12%, Connective Tissue - 10%
50	274551.1.oct	Nervous System - 60%, Hemic and Immune System - 40%
51	411408.20.dec	Connective Tissue - 12%, Cardiovascular System - 11%
52	035973.1.dec	Embryonic Structures - 67%, Nervous System - 17%, Digestive System - 17%
53	456536.1.dec	widely distributed
54	387807.4.oct	Sense Organs - 33%, Skin - 11%, Male Genitalia - 10%
55	406790.3.dec	Unclassified/Mixed - 32%, Urinary Tract - 25%, Musculoskeletal System - 10%
56	412420.63.dec	Sense Organs - 40%
57	196623.3.dec	widely distributed
58	427916.8.dec	Nervous System - 100%
59	264633.8.dec	Embryonic Structures - 86%, Hemic and Immune System - 14%
61	902943.1.dec	Unclassified/Mixed - 38%, Female Genitalia - 19%, Respiratory System - 10%
64	197445.1.oct	Unclassified/Mixed - 28%
65	348775.1.oct	Skin - 28%, Connective Tissue - 15%, Nervous System - 15%
66	336239.5.dec	Hemic and Immune System - 100%
67	215660.4.dec	Nervous System - 100%
68	391940.2.dec	Hemic and Immune System - 58%, Male Genitalia - 26%, Respiratory System - 16%
69	978302.3.dec	Sense Organs - 16%, Germ Cells - 11%, Embryonic Structures - 11%
70	228629.11.dec	Digestive System - 60%, Hemic and Immune System - 40%
71	011211.5.dec	Musculoskeletal System - 32%, Endocrine System - 27%, Nervous System - 18%

Table 6

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	PE Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	PE Biosystems, Foster City, CA;	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	PE Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25:3389-3402.	ESTs: Probability value= 1.0E-8 or less; Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. USA 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183:63-98; and Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.06E-6; Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less; Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff (1991) Nucleic Acids Res. 19:6565-6572; Henikoff, J.G. and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37:417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol. 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 6

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221.	Normalized quality score≥GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M.S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies.	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12:431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

CLAIMS

What is claimed is:

1. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71,

b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71,

c) a polynucleotide sequence complementary to a),

d) a polynucleotide sequence complementary to b), and

e) an RNA equivalent of a) through d).

2. An isolated polynucleotide of claim 1, comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:1-71.

3. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 1.

4. A composition for the detection of expression of diagnostic and therapeutic polynucleotides comprising at least one of the polynucleotides of claim 1 and a detectable label.

5. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 1, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

6. A method for detecting a target polynucleotide in a sample, said target polynucleotide comprising a sequence of a polynucleotide of claim 1, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe

specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

7. A method of claim 5, wherein the probe comprises at least 30 contiguous nucleotides.

8. A method of claim 5, wherein the probe comprises at least 60 contiguous nucleotides.

9. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 1.

10. A cell transformed with a recombinant polynucleotide of claim 9.

11. A transgenic organism comprising a recombinant polynucleotide of claim 9.

12. A method for producing a diagnostic and therapeutic polypeptide, the method comprising:

a) culturing a cell under conditions suitable for expression of the diagnostic and therapeutic polypeptide, wherein said cell is transformed with a recombinant polynucleotide of claim 9, and:

b) recovering the diagnostic and therapeutic polypeptide so expressed.

13. A purified diagnostic and therapeutic polypeptide encoded by at least one of the polynucleotides of claim 2.

14. An isolated antibody which specifically binds to a diagnostic and therapeutic polypeptide of claim 13.

15. A method of identifying a test compound which specifically binds to the diagnostic and therapeutic polypeptide of claim 13, the method comprising the steps of:

a) providing a test compound;

b) combining the diagnostic and therapeutic polypeptide with the test compound for a sufficient time and under suitable conditions for binding; and

c) detecting binding of the diagnostic and therapeutic polypeptide to the test compound, thereby identifying the test compound which specifically binds the diagnostic and therapeutic polypeptide.

16. A microarray wherein at least one element of the microarray is a polynucleotide of claim 3.

17. A method for generating a transcript image of a sample which contains polynucleotides, the method comprising the steps of:

a) labeling the polynucleotides of the sample,

b) contacting the elements of the microarray of claim 16 with the labeled polynucleotides of the sample under conditions suitable for the formation of a hybridization complex, and

c) quantifying the expression of the polynucleotides in the sample.

18. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a polynucleotide sequence of claim 1, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,

b) detecting altered expression of the target polynucleotide, and

c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

19. A method for assessing toxicity of a test compound, said method comprising:

a) treating a biological sample containing nucleic acids with the test compound;

b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 1 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 1 or fragment thereof;

c) quantifying the amount of hybridization complex; and

d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

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[Continued on next page]

(54) **Title:** MOLECULES FOR DIAGNOSTICS AND THERAPEUTICS

(57) **Abstract:** The present invention provides purified human polynucleotides for diagnostics and therapeutics (dithp). Also encompassed are the polypeptides (DITHP) encoded by dithp. The invention also provides for the use of dithp, or complements, oligonucleotides, or fragments thereof in diagnostic assays. The invention further provides for vectors and host cells containing dithp for the expression of DITHP. The invention additionally provides for the use of isolated and purified DITHP to induce antibodies and to screen libraries of compounds and the use of anti-DITHP antibodies in diagnostic assays. Also provided are microarrays containing dithp and methods of use.

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(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Docket No.: PT-1066 USN

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

MOLECULES FOR DIAGNOSTICS AND THERAPEUTICS

the specification of which:

/___/ is attached hereto.

/___/ was filed on ______________ as application Serial No. ______________ and if this box contains an X /___/, was amended on ______________________________.

/ X / was filed as Patent Cooperation Treaty international application No. PCT/US00/25643 on September 19, 2000, if this box contains an X /_/, was amended on under Patent Cooperation Treaty Article 19 on ______ 2001, and if this box contains an X /_/, was amended on ________________.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge my duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim the benefit under Title 35, United States Code, §119 or §365(a)-(b) of any foreign application(s) for patent or inventor's certificate indicated below and of any Patent Cooperation Treaty international applications(s) designating at least one country other than the United States indicated below and have also identified below any foreign application(s) for patent or inventor's certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application for said subject matter the priority of which is claimed:

Country	Number	Filing Date	Priority Claimed
____________	____________	____________	/_/ Yes /_/ No
____________	____________	____________	/_/ Yes /_/ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Application Serial No.	Filed	Status (Pending, Abandoned, Patented)
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60/155,760	9/23/99	Expired
60/155,939	9/24/99	Expired
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60/156,625	9/28/99	Expired
60/167,542	11/24/99	Expired
60/167,522	11/24/99	Expired
60/167,453	11/24/99	Expired
60/167,517	11/24/99	Expired
60/167,943	11/25/99	Expired
60/167,945	11/25/99	Expired
60/167,520	11/24/99	Expired
60/168,468	12/1/99	Expired
60/168,599	12/1/99	Expired
60/167,410	11/24/99	Expired
60/168,265	11/30/99	Expired
60/168,429	11/30/99	Expired
60/168,432	11/30/99	Expired
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60/168,857	12/2/99	Expired
60/168,197	11/30/99	Expired
60/168,611	12/2/99	Expired
60/168,613	12/2/99	Expired

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of Title 35, United States Code §112, I acknowledge my duty to disclose material information as defined in Title 37 Code of Federal Regulations, §1.56(a) which occurred between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

Application Serial No.	Filed	Status (Pending, Abandoned, Patented)

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respectively and individually, as my patent attorneys and/or agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Docket No.: PT-1066 USN

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Docket No.: PT-1066 USN

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Docket No.: PT-1066 USN

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Docket No.: PT-1066 USN

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DUFOUR, Gerard E.
COHEN, Howard J.
ROSEN, Bruce H.
SHAH, Purvi
CHALUP, Michael S.
HILLMAN, Jennifer L.
JONES, Anissa L.
YU, Jimmy Y.
GREENAWALT, Lila B.
PANZER, Scott R.
ROSEBERRY, Ann M.
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<213> Homo sapiens

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<213> Homo sapiens

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<212> DNA
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<221> unsure
<222> 2042
<223> a, t, c, g, or other

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<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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<213> Homo sapiens

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<223> Incyte ID No: 899943.1.dec

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<213> Homo sapiens

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<213> Homo sapiens

<220>
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<223> Incyte ID No: 897957.1.dec

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<221> unsure
<222> 64, 71
<223> a, t, c, g, or other

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<212> DNA
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<211> 577
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 442286.1.dec

<400> 26
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ggggagaagg gcggaggcaa agccgaggag gtgcgggttg tggtccattc tggaggacgc 180
tgatcgaatg ccccaaactt cccggaatgt gtgtggaccc ttctagcctg aggagtcctg 240
caggtgtgaa gctccacacc tgcctccata gcactttgcc tgtccctaag agggctcatc 300
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gccctgtaca gggacgtgat gctggagaac tacagcaacc tggtctcact gggactctta 480
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<210> 27

<211> 1349
<212> DNA
<213> Homo sapiens

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<220>
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<222> 1267, 1324, 1329, 1341
<223> a, t, c, g, or other

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gcttggtggc ctttgaggat gtggcagtga acttcaccca ggaggagtgg gctttgctgg 300
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tggnttgant tactgcaggg ncttctgga 1349

<210> 28
<211> 1696
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 479346.1.dec

<220>
<221> unsure
<222> 1089, 1237, 1283
<223> a, t, c, g, or other

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gaggaggttc ctggatgtgg atgtcatcat ttctgggaac actcttaaat ggagactcag 180
atttcttagc caaaatttag ggaggatcca gaagaaacca aagacgaagc atcccagttc 240
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ccctttgtat gtcctg 1696

<210> 29
<211> 2459
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 481750.1.dec

<400> 29
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tatctgggcc tggaaaaaat gtaccactta cattgaattt gctcttcaac ccacaggttc 180
tgactcctca ggagcaaaaa acataacctg aagagggagg aagtggattt ggggttcacc 240
atttcttggg gcacacttga ttgaaaactg agacttctga agagaaggcc agaagataca 300
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<210> 30
<211> 469
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 900917.2.dec

<400> 30
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cacctagatt cataagctgc cctgaggcga tcttggcatc aagaaagaca gcattgaggc 180
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<210> 31
<211> 682
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 999415.1.dec

<220>
<221> unsure
<222> 382
<223> a, t, c, g, or other

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gaaaatgaga acaatataat gaaccctaaa ggagatagct ctatttatat tgaaaatcaa 600
gagtttccat tttggagaac ccagcattct tgcgggaata catatctgag tgagtcacag 660
attcagagta gaggtaagca aa 682

<210> 32
<211> 996
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 900680.2.dec

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<210> 33
<211> 2098
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 902791.3.dec

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<210> 34
<211> 1520
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 053826.1.dec

<220>
<221> unsure
<222> 1479
<223> a, t, c, g, or other

<400> 34
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<210> 35
<211> 1722
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 204932.4.dec

<220>
<221> unsure
<222> 45
<223> a, t, c, g, or other

<400> 35
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<222> 1653
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<213> Homo sapiens

<220>
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<211> 574
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<220>
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catgttgcca tgcagagaaa gaga 444

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<220>
<221> unsure
<222> 1195
<223> a, t, c, g, or other

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<212> DNA
<213> Homo sapiens

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<211> 279
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<213> Homo sapiens

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<211> 1038
<212> DNA
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<211> 457
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 427916.8.dec

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<221> unsure
<222> 398
<223> a, t, c, g, or other

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<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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